FORMULATION AND *IN-VITRO* EVALUATION OF MEBEVERINE HYDROCHLORIDE COLON TARGETED MICROPELLETS FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

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Submitted by

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CERTIFICATE

This is to certify that the research work entitled "**FORMULATION AND *IN-VITRO* EVALUATION OF MEBEVERINE HYDROCHLORIDE COLON TARGETED MICROPELLETS FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME"** submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **"SOWJANYA.M" (Register No. 26106018)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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Dedicated

To

My beloved parents...

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SOWJANYA.M

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ABBREVIATIONS

%	----	Percentage
<	----	Less Than
>	----	More Than
°C	----	Degree Celsius
µg	----	Microgram
cm	----	Centimeter
CTDDS	----	Colon targeted drug delivery system
DE	----	Dissolution Efficiency
DSC	----	Differential Scanning Calorimetry
F	----	Formulation
FTIR	----	Fourier Transform-Infra Red Spectroscopy
GIT	----	Gastrointestinal Tract
gm	----	Grams
HCl	----	Hydrochloric acid
HPMC	----	Hydroxypropyl methylcellulose
hrs	----	Hours
IBS	----	Irritable Bowel Syndrome
ICH	----	International Conference on Harmonization
IP	----	Indian Pharmacopoeia
LSC	----	Loose surface crystal

MDT	----	Mean Dissolution Time
mg	----	Milligram
ml	----	Milli liter
mm	----	Millimeter
N	----	Normality
nm	----	Nanometer
NSAID	----	Non-Steroidal Anti-Inflammatory Drugs
PBS	----	Phosphate Buffer Solution
RH	----	Relative Humidity
rpm	----	Revolutions per Minute
S. No.	----	Serial Number
SEM	----	Scanning electron microscope
T	----	Time
USP	----	United State Pharmacopoeia
UV	----	Ultra Violet
W/v	----	weight/volume
λ max	----	Absorption maximum

INTRODUCTION...

1. INTRODUCTION

1.1. COLON TARGETED DRUG DELIVERY SYSTEM

(Asha patel et al., 2011).

Colon is being extensively investigated as a drug delivery site. Colon targeted drug delivery system (CTDDS) has been developed by means of one or more controlled released mechanisms. It is convenient for treating localized colonic diseases, i.e. Ulcerative colitis, Crohn's diseases and constipation etc.

Its potential applications include Chronotherapy, Prophylaxis of colon cancer and treatment of Nicotine addiction. The treatment of Inflammatory Bowel Disease (IBD) with anti inflammatory drugs is particularly improved by local delivery to bowel by using CTDDS. For successful colon specific drug delivery, many physiological barriers must be overcome; the major one is being absorption or degradation of the active drug in the upper part of the GIT. The minor is disease state, which can potentially alter the delivery and absorption characteristics of drugs from the colon.

The CTDDS should protect the drug from the absorption and degradation in the stomach and small intestine, the drug should be absorbed only at the colonic site. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is a suitable absorption site for peptides and protein drugs.

1.1.1. Need Of Targeting:

- It ensures direct treatment at the disease site, lower dosing and fewer systemic side effects.
- It allows oral administration of peptide and protein drugs.
- Both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease.
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

1.1.2. Therapeutic Advantages of Targeting:

It offers the following therapeutic advantages:

- Minimizing extensive first pass metabolism of steroids.
- Preventing the gastric irritation produced by oral administration of NSAIDS.
- Improved therapy of diseases susceptible to diurnal rhythm.
- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.
- Potential for oral delivery of proteins, peptides and other GI liable drugs.
- By producing the 'friendlier' for peptides and proteins when compared to upper GI tract.

The therapy of various disease conditions can be improved by colon specific drug delivery systems employing various mechanisms of release, which is shown in

Table 1: Showing target sites and disease occurs at sites.

Target site	Disease condition	Drugs and Active agents
TOPICAL ACTION	Inflammatory Bowel disease, Irritable bowel Syndrome, Chronic Pancreatitis, and Crohn's disease.	Hydrocortisone, Budenoside,Prednisolone,Sulfasalazine, Olsalazine, Mesalazine and Balsalazide.
LOCAL ACTION	Pancreoctomy and Crystal fibrosis, Colorectal cancer	Digestive enzymes supplements, 5-Flourouracil.
SYSTEMIC ACTION	To prevent gastric irritation To prevent first pass metabolism for orally ingested drugs Orally delivered peptides Orally delivered vaccines	NSAIDS Steroids Insulin Typhoid

Delayed systemic absorption of drugs via colonic delivery is advisable for Chronotherapy of diseases such as asthma, hypertension, cardiac arrhythmias, rheumatoid arthritis or inflammation, which are affected by circadian rhythms. These diseases are characterized by night time or early smorning symptoms. These types of approaches are beneficial for nocturnal release of drug, which in turn may provide considerable relief to the patients while they are resting.

The mode of drug release from colon-targeted biopolymer systems can include one or more of the following mechanisms

1. Diffusion
2. Polymer erosion
3. Microbial degradation
4. Enzymatic degradation (mammalian and/or bacterial)

In addition, drug solubility and formulation of polymer mixes play important roles in determining the extent of drug delivery and release in the colon.

Two broad categories of biopolymers have been employed for formulating colonic systems:

(1) Biodegradable and

(2) Non biodegradable polymers

1.1.3. Limitations of Colon targeting:

To achieve successful colon targeting it should overcome the following limitations

The location at the distal portion of the alimentary canal, the colon is difficult to access.

- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.

1.1.4. General considerations for designing of colon targeting formulations:

To achieve a desired therapeutic action of dosage form, it is necessary to design a suitable formulation with suitable qualities. In general, delayed release dosage forms are designed to provide a burst release or a sustained/ prolonged release once they reach colon.

Various factors includes are

- Pathology and pattern of diseases, especially the affected parts of lower GIT or, Physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.
- Physicochemical properties and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and the desired release profile of the active ingredient.

Formulation of drugs for colon specific delivery requires careful consideration of dissolution of and / or release rate in the colon fluids. Due to the presence of less fluid content in large intestine than in small intestine the dissolution and release rate from the formulations decreases. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water soluble and / or require higher doses for therapy. Consequently, such drugs need to be delivered in pre solubilized form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general fecal matter, thereby reducing the concentration of

free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.

1.2. General anatomy and physiology of colon:

(Akhil guptha et al., 2011)

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal.

The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the caecum, ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in Table 2. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid.

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of fecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material

equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria .The colon tissue containing the vile, lymph, muscle, nerves, vessels.

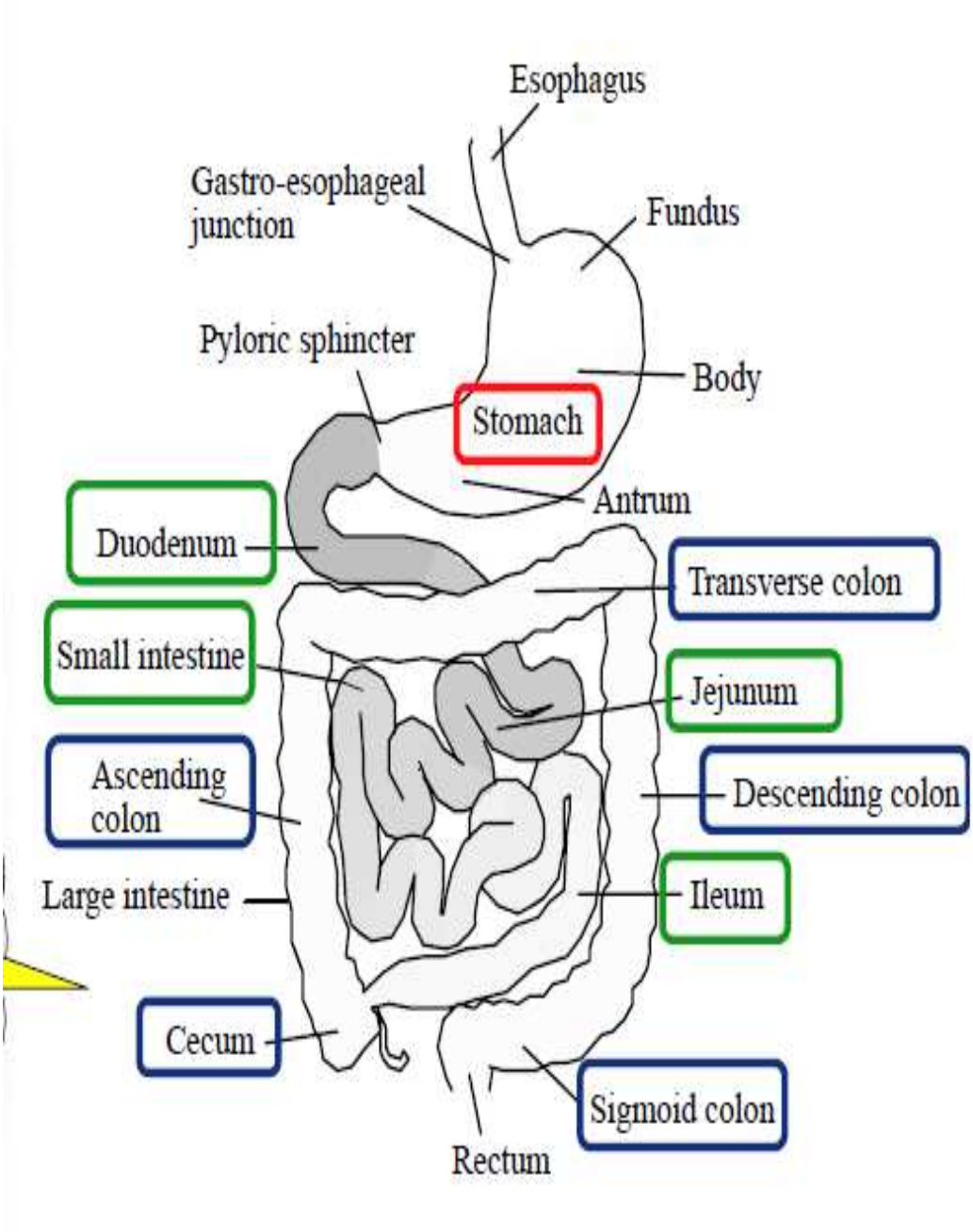


Fig. 1: Anatomy of the three parts of colon

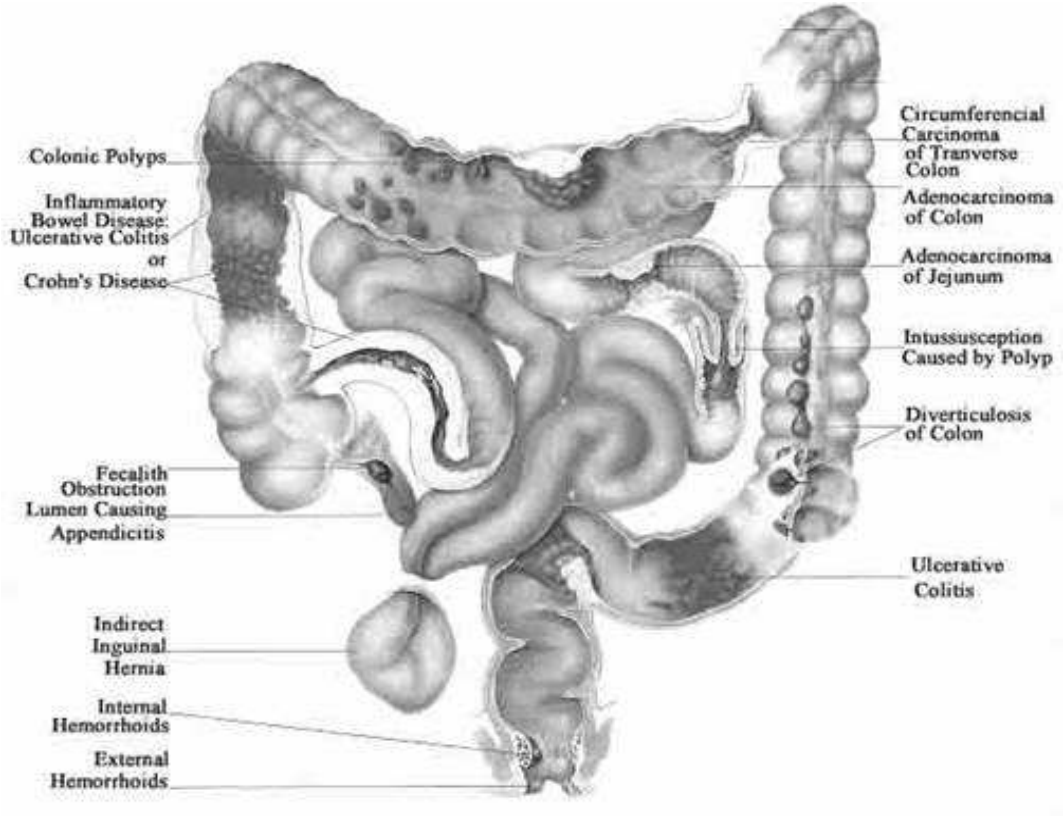


Fig. 2: Main features of the colon

Different properties of GIT were given in (Table 2) and different enzymes present in colon, which are responsible for microbial degradation, were reported by Vincent et al (2002).

Table 2: Properties of Gastro Intestinal Tract:

S.No.	Region of GIT	Property	Measured value(cm)
1	Total GIT	Surface area	2-106
2	Small intestine -Duodenum -Jejunum -Ileum	Length	 20-30 150-250 200-350
3	Large intestine -Cecum -Ascending colon -Descending colon -Transverse colon -Sigmoid colon -Rectum -Anal canal	Length	 6-7 20 45 30 40 12 3
4	 Small intestine Large intestine	Internal diameter	 3-4 6
5	Stomach Duodenum Jejunum Ileum Colon Rectum	PH	1 3.5 5-7 6-7 7 5.5-7 7
6	Colon -Right -Mid -Left	Redox potential	- 415 - 400 - 380

1.2.1. Gastrointestinal transit Time:

Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The transit times of dosage forms in tract are shown in Table 3.

Table 3: Gastrointestinal Transit time of contents:

Organ	Transit Time (hr)
Stomach	<1(fasting)>3(fed)
Small intestine	3-4
Large intestine	20-30

1.3. Pharmaceutical approaches for CTDDS:

(Akhil guptha et al., 2011)

Various pharmaceutical approaches that can be exploited for the development of colon targeted drug delivery systems are given below:

Approaches used for site specific drug delivery are

- **Primary approaches for CTDDS:**
- P^H sensitive polymer coating drug delivery to colon.
- Delayed (time controlled release system) release drug delivery to colon.
- Microbially triggered drug delivery to colon.

  i) Prodrug approach for drug delivery to colon.

  ii) Azo – polymeric approach for drug delivery to colon

  iii) Polysaccharide based approach for drug delivery to colon.

❖ **Newly developed approaches for CTDDS:**

- Pressure controlled drug delivery system (PCDCS)
- CODESTM (a novel colon targeted delivery system)
- Osmotic controlled drug delivery to colon (OROS – CT)
- Pulsincap system
- Port system
- Time clock system
- Chronotropic system
- Colal – Pred system
- Target technology
- Ticking capsule
- Enterion capsule technology

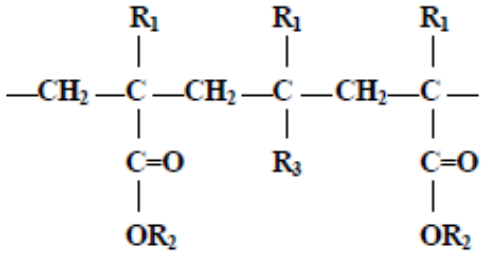
1.3.1. Primary Approaches:

1.3.1.1. pH Dependent Systems:

The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increase to 4 during digestion), small intestine (pH 6 - 7) at the site of digestion and it increases to 7-8 in the distal ileum. The gamma scintigraphy technique becomes most popular technique to investigate the gastrointestinal performance of pharmaceutical formulations. The pH sensitive polymers (given in Table 4) which will produce delayed release and also give protection from gastric fluids.

Table 4: List of Enteric Polymers used in the development of Modified-Release Formulations for Colonic drug Delivery systems

S.No.	Enteric Polymers	Optimum pH for dissolution
1	Polyvinyl acetate phthalate (PVAP)	5.0
2	Cellulose acetate tri melitate (CAT)	5.5
3	Hydroxypropyl methylcellulose phthalate (HPMCP)	> 5.5
4	Hydroxy propyl methylcellulose acetate succinate (HPMCAS)	> 6.0
5	Methacrylie acid copolymer, Type C (Eudragit L100-55)	> 6.0
6	Methacrylic acid copolymer dispersion (Eudragit L30D-55)	> 5
7	Methacrylic acid copolymer, Type A	> 6.0
8	(Eudragit®L-100 and Eudragist L12,5)	_
9	Cellulose acetate phthalate (CAP) (Aquateric)	6.0
10	Methacrylic acid copolymer, Type B	> 7.0
11	(Eudragist S-100 and Eudragit S12,5)	_
12	Eudragit FS30D	> 7.0
13	Shellac (MarCoat 125 &125N)	7.0



$R_1 = -CH_3$, $R_2 = -CH_3$ and $R_3 = -COOH$ (Eudragit® L and S)
$R_1 = -CH_3$, $R_2 = -CH_2-CH_3$ and $R_3 = -COOH$ (Eudragit® L100-55 and L30D-55)
$R_1 = -CH_3$, $R_2 = -CH_3$ and $R_3 = -COOCH_3$ (Eudragit® NE30D)
$R_1 = -CH_3$, $R_2 = -CH_3$ and $R_3 = -COOCH_2CH_2N^+(CH_3)_3Cl^-$ (Eudragit® RL and RS)

Fig.3: Chemical structure of Eudragit

The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine. Methacrylic acid esters most commonly used polymers for colon targeting because they are soluble at above pH 6. The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit-L and Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 or above and Eudragit S is soluble at pH 7 or above and the combination of these polymers give the desirable release rates. The polymers of this class are insoluble at low P^H levels but become increasingly soluble as P^H rises. The polymers of this class protect the formulation from the acidic P^H and proximal small intestine, it may start to dissolve in the lower small intestine, and the site specificity of formulations can be poor. P^H-sensitive hydro gels were prepared for colonic delivery of therapeutic peptides, proteins. New pH-sensitive glycopolymers were developed by free radical polymerization of Methacrylic acid and 6-hexandiol diacrylate

and 6- hexandiol propoxylate diacrylate. Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen, Khan *et al*. prepared lactose-based placebo tablets and coated using various combinations of two methacrylic acid polymers, Eudragit L100-55 and Eudragit S100 by spraying from aqueous systems. The same coating formulations are then applied on tablets and evaluated for *in vitro* dissolution rates under various conditions.

1.3.1.2. Time-Dependent Systems:

1. Time dependent systems are very promising type of drug release systems. The dosage forms also applicable to colon targeting dosage forms by prolonging the lag time of about 5 to 6 hours.

2. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

3. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

4. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the characinoid syndrome and diarrhea, and the ulcerative colitis.

Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount. Enteric coated time-release press coated (ETP) tablets, are

composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy Propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer.

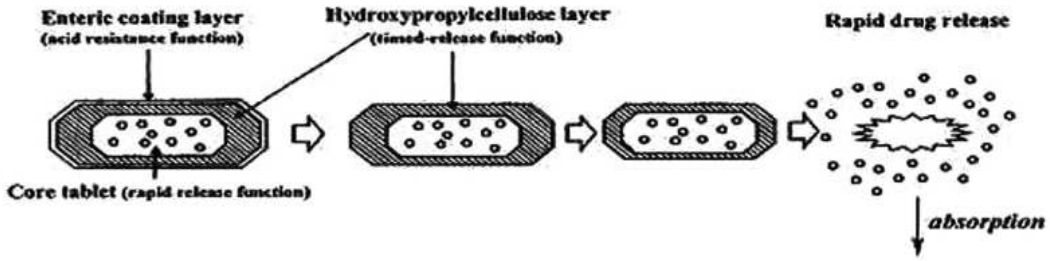


Fig. 4: Design of enteric coated timed-release press coated tablet (ETP Tablet)

A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required disperse in aqueous environment Hydroxy Propyl Methyl Cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then coated with 50% of HPMC/lactose coat powder by compression-coating method. Drug release

characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method.

1.3.1.3. Micro Flora Activated System:

A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. Over 400 distinct bacterial species have been found, 20- 30% of which are of the genus bactericides. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive facultative bacteria. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source.

Table 5: The human gastro-intestinal flora:

	Stomach	**Jejunum**	**Ileum**	**Feces**
Total bacterial count	$0\text{-}10^3$	$0\text{-}10^5$	$10^3\text{-}10^7$	$10^{12}\text{-}10^{12}$
Anaerobic bacteria				
E.Coli	$0\text{-}10^2$	$0\text{-}10^3$	$10^2\text{-}10^6$	$10^4\text{-}10^{10}$
Strepto cocci	$0\text{-}10^3$	$0\text{-}10^4$	$10^2\text{-}10^6$	$10^5\text{-}10^{10}$
Staphylo cocci	$0\text{-}10^2$	$0\text{-}10^3$	$10^2\text{-}10^5$	$10^4\text{-}10^7$
Lactobacilli	$0\text{-}10^3$	$0\text{-}10^4$	$10^2\text{-}10^5$	$10^6\text{-}10^{10}$
Fungi	$0\text{-}10^2$	$0\text{-}10^2$	$10^2\text{-}10^3$	$10^2\text{-}10^6$
Anaerobic bacteria				
Bacteroids	Rare	$0\text{-}10^2$	$10^3\text{-}10^5$	$10^{10}\text{-}10^{12}$
Bifid bacteria	Rare	$0\text{-}10^3$	$10^3\text{-}10^7$	$10^8\text{-}10^{12}$

The metabolic activity of micro flora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues

1.3.1.3.1. Prodrug approach:

A Prodrug is a pharmacologically inactive derivative of a parent compound that requires enzymatic transformations in order to release the drug and that has improved release properties over the parent compound. Formulation of Prodrug has improved delivery properties over the parent compound. The choice of carrier is largely determined by the functional group available on the drugs.There are at least three factors should be optimized for the site specific delivery of drugs by using the Prodrug approach.

1. The Prodrug must to reach the target for the site of action as early as possible, and uptake from the site must be fast and essentially perfusion rate limited.
2. Once the drug reached to the site, Prodrug must be selectively liberated to the active drug relative to its conversion at other sites.
3. Once selectively liberated at the site of action, the active drug must be somewhat retained by the tissue.

The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by Pro drugs formation, which is converted into parent drug molecule once it reaches to colon. Enzymes produced by bacterial flora, which are responsible for the cleavage of Prodrug, are listed in Table

Table 6: Enzymes in Colon:

S.No.	Type	Examples
1	**Reducing enzymes**	Nitroreductase Azoreductases N-oxide reductase Sulphoxide reductase Hydrogenase
2	**Hydrolytic enzymes**	Esterasess Acidizes Glycosidase Glucuronidase Sulfites

1.3.1.3.2. Azo-Prodrugs:

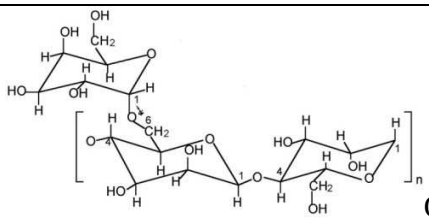
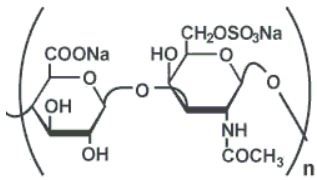
One of the first prodrugs on the market that used colonic enzymatic biodegradation as its active principle was sulfasalazine (salazosulfapyridine) and the other modern successor products are olsalazine, balsalazine, and ipsaslazine, all of them used for the treatment of inflammatory bowel diseases and containing two molecules linked by an azo bond. The prodrugs pass the stomach and the small intestine unchanged and unabsorbed. Reaching the caecum, they are reduced and cleaved by specific azoreductases of the microflora[20]. During this process of enzymatic decomposition, the drug is released in a micro-fine physical state that promotes rapid and extensive dispersion, and thus guarantees maximal topical and systemic activity.

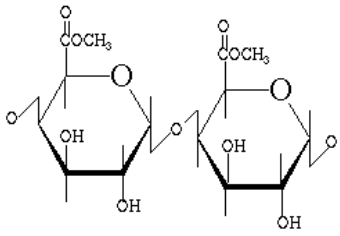
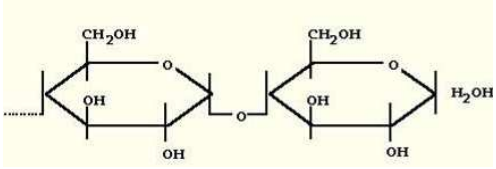
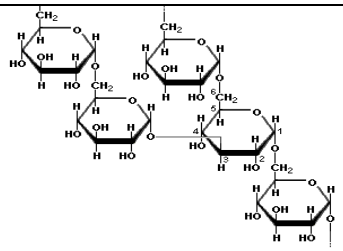
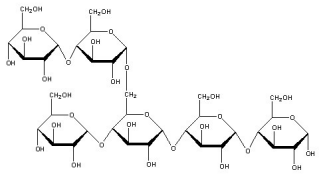
1.3.1.3.3. Polysaccharide based delivery system:

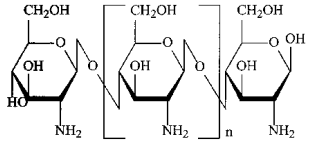
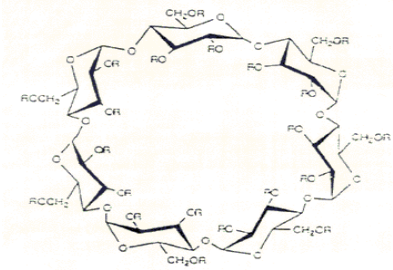
Use of natural occurring polysaccharides is of attention for drug targeting to coon since these polymers of monosaccharide's are found in abundance, have wide availability are inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically and biochemically and are highly stable, nontoxic,

hydrophobic and gel forming and in addition biodegradable. These include naturally occurring polysaccharides obtained from plant, animal (chytosan, chondiotin sulphate), argal (alginates) as microbial origin. These are broken down by colonic micro flora to simple saccharides. So these falls into category of "generally regarded as safe" (GRAS) polysaccharide based delivery system have outlined in table 7.

Table 7: List of Natural polymers (Polysaccharide Approach) used in colon specific drug delivery

Polymer	Structure	Comments
Guar Gum	 Galactomannan polysaccharide (β-1,4 D-mannose, α-1,6 D-galactose) having (1-4) linkage	It has low water solubility but hydrates and swells in cold water forming viscous colloidal dispersions or solutions.
Chondroitin Sulfate	 Mucopolysaccharide consisting of β-1,3 D-glucuronic acid linked to N-acetyl-D-galactosamide	It is readily water soluble. So it is used with combination of nonbiodegradable swelling polymers.

Pectin	 α-1,4 D-galacturonic acid and 1,2 L-rhamnose with D-galactose and L-arabinose side chains	Calcium and Zinc crosslinked Pectin have more drug retention property when compared to Pectin.
Amylose	 Liner polymer of glucopyranose units (α-1,4 D-glucose) linked through α–D-(1,4)-linkages	Amylose is resistant to pancreatic amylases.
Dextran	 It consists of α-1,6 D-glucose and α-1,3 D-glucose units	Daxtran hydrogels are stable in the presence of small intestinal enzymes amyloglucosidase, invertase, and pancreatin.
Starch	 It consists of amylase and amylopectin	Starch is hydrolysed by several amylolytic enzymes in the gut. A colon drug delivery composition has been

		described using starch capsules to contain the drug followed with pH sensitive material or colonic microbial enzyme degradable coating.
Chitosin	 Poly (2-amino 2-deoxy D-glucopyranose) in which the repeating units are linked by (1-4) β-bonds	It dissolves in the acidic pH of the stomach but swells at pH 6.8, so enteric coating is required.
Cyclodextrin	 It consists of at least six glucopyranose units joined by α- (1-4) linkage	Cyclodextrins can be fermented to small saccharides by colonic microflora, whereas they are only slowly hydrolysable in the conditions of the upper gastrointestinal tract.

1.3.2. Newly Developed Approaches for CTDDS:

1.3.2.1. Pressure Controlled Drug-Delivery Systems:

It is due to peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules using ethyl cellulose, which is insoluble in water. In such systems, drug release occurs followed by disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is an important factor for the disintegration of the formulation .The system also depends on capsule size and density. Because of re absorption of water from the colon, the viscosity of luminal content is greater in the colon than in the small intestine. It is therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethyl cellulose single unit capsules the drug is in a liquid form. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

1.3.2.2. Novel Colon Targeted Delivery System (CODESTM):

CODESTM is a unique CTDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbial triggered CTDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon.

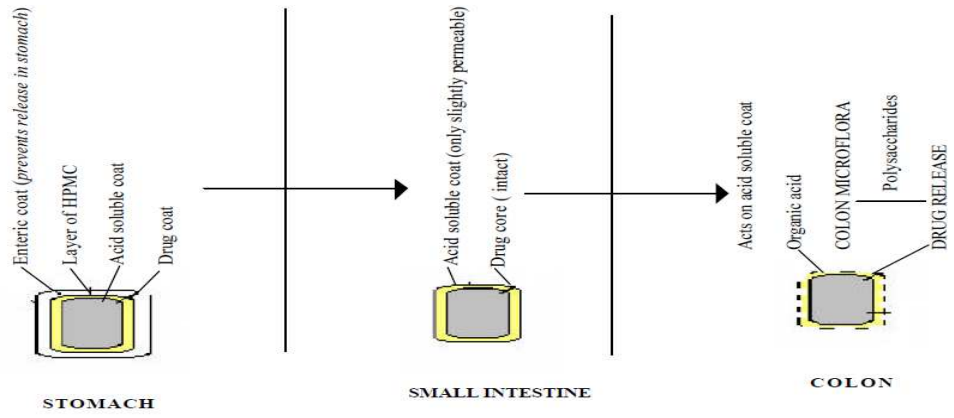


Fig .5: Schematics of the conceptual design of CODES

The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.

1.3.2.3. Osmotic Controlled Drug Delivery (OROS-CT):

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable .The OROS-CT system can be a single osmotic unit or may incorporate as

many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, · Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CTDDS.

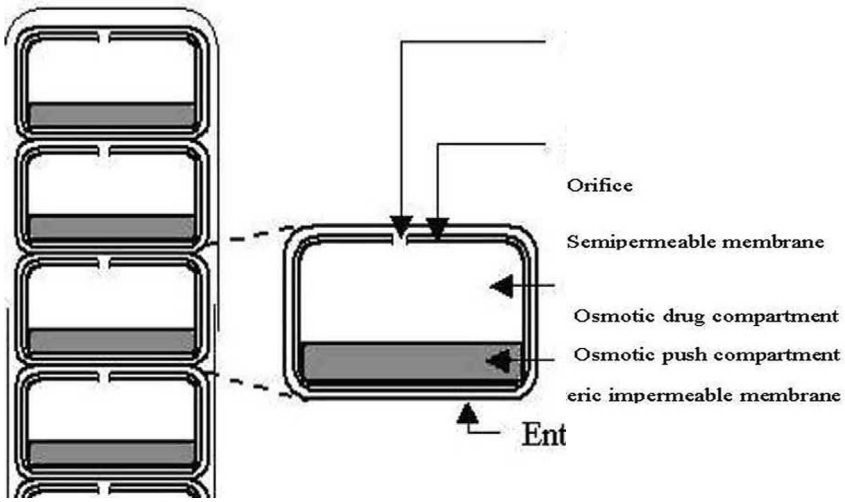


Fig.6: Cross-Section of the OROS colon targeted drug delivery system

These days the basic CTDDS approaches are applied to formulate novel drug delivery systems. Such as Multiparticulate systems, Microspheres, Liposomes, Microencapsulated particles, Micro pellets etc.

1.3.2.4. Pulsatile system:

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form and it also releases drug in constant or variable rates. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form. Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid and complete release of loaded drugs. The

approach is based on the principle of delaying the time of drug release until the system transits from mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered.

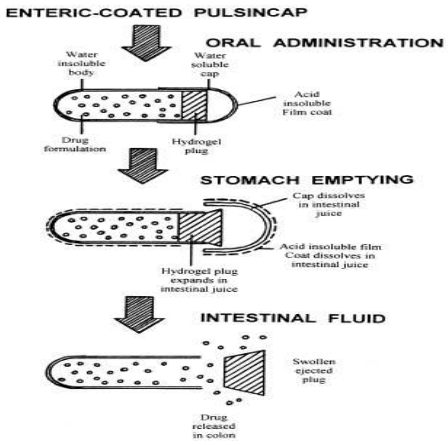


Fig. 7: Enteric coated pulsing cap

1.3.2.5. Port System:

The Port system was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable membrane (Figure 8) inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. System shows good *in-vivo* and *in-vitro* correlation in humans and used to deliver methylphenidate to school age children for the treatment of attention deficit hyperactivity disorder (ADHD).

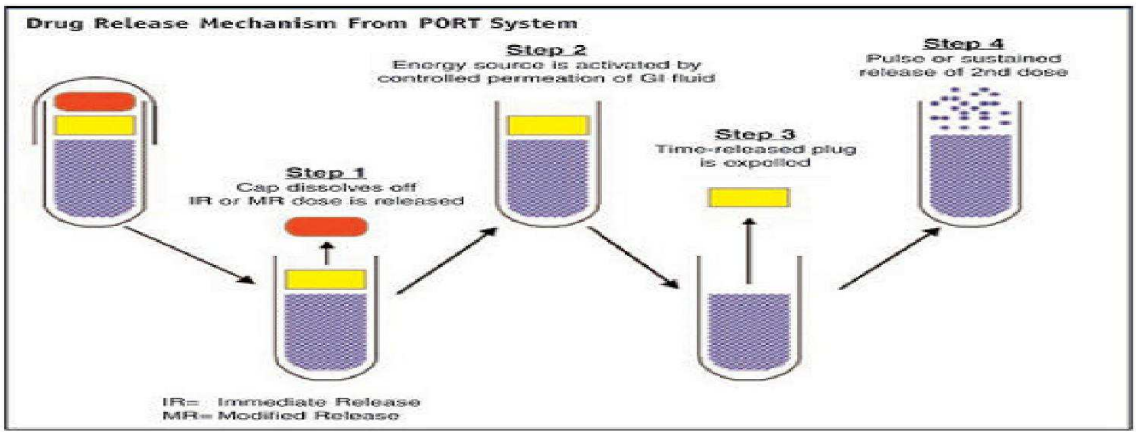


Fig.8: Design of PORT system

1.3.2.6. Time clock:

In this, drug releases after a predetermined lag time. The lag time usually starts after gastric emptying because most of the time-controlled formulations are enteric coated. Drug release from these systems is not p^H dependent.

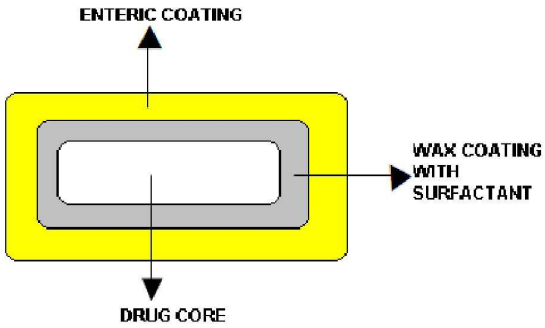


Fig.9: Design of Time clock system

1.3.2.7. Chronotropic system:

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and the drug releases at once after this lag time. Chronotropic system consists of a core containing reservoir coated by a hydrophilic polymer HPMC. An additional enteric-coated film is given outside this layer to overcome

intra subject variability in gastric emptying rates (Figure 10).The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC.

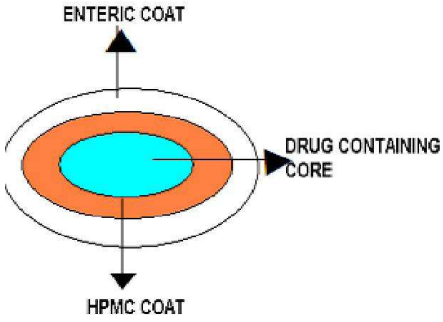


Fig .10: Design of Chronotropic system

1.3.2.8. Colol-Pred System:

COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It has arisen from combining Alizyme's properitary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium Meta sulfo benzoate). It is an effective anti inflammatory treatment for UC without the typical side effects of steroids. There are currently no competitor products, either on the market or in development, with the same profile of product. A 'Safe steroid' product with the profile of

COLAL-PRED would represent a significant advance in the management of UC. COLALPRED has a coating that is broken down only in the colon, by locally occurring bacteria. This leads to topical delivery of prednisolone to the colon without significant systemic exposure so minimizing steroid related side effects.

1.3.2.9. Targit Technology:

TARGIT Technology (West Pharmaceutical services) is designed for site-specific delivery of drugs in the gastrointestinal (GI) tract and, in particular, targeted release into the colonic region. A key area of application is the delivery of therapeutic agents for local treatment of lower GI diseases. The technology is based on the application of pH-Sensitive coatings onto injection-moulded starch capsules. An extensive body of clinical data has been generated showing reliable in vivo performance of the capsules. In Y-Scintigraphy studies, around 90% of TARGIT Capsules (n=84) delivered their contents to the target site of the terminal ileum and colon. TARGIT based products are in active clinical development for the treatment of conditions including inflammatory bowel diseases.

1.3.2.10. Ticking capsule:

It is a chronotherapeutic devices employ some electrical means of controlling pulsatile drug release coupled with electronic timing. Ticking capsules is divided into three compartments; Porous Si-based drug delivery module; Electronic control module (e.g. mucontroller) and Battery. (Figure 12) Many human illnesses and their Symptoms show a regular (rhythmic) pattern: Hypertension (early morning); arthritics pain (mid afternoon); heart attack (early morning + late afternoon and asthma attack (night). It is recognizing intake into the body is limed to match the severity of the Symptom.

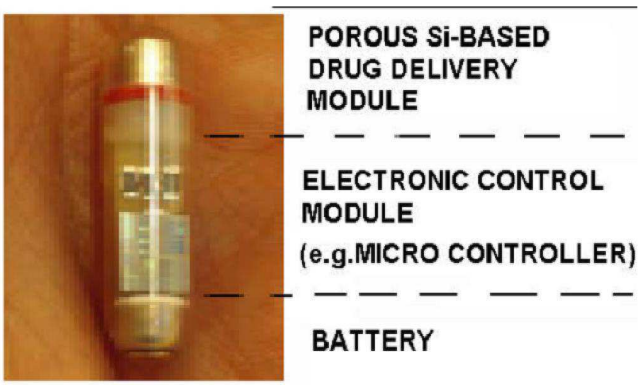


Fig.11: Design of ticking capsule system

1.3.2.11. Enterion capsule Technology:

The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut (Fig-12). It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule can be loaded with either a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in sit affects etc.) through an opening 9 mm in diameter, which is then sealed by inserting a push-on Cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament.

Fig. 12: Design of Enterion capsule

A radioactive marker is placed inside a separate sealed tracer port to allow real time visualization of the capsule location using the imaging technique of gamma Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic field is set in the low MHz region, low enough so that there is negligible absorption of the energy by the body tissues but sufficiently high enough to induce unable power in a tuned coil antenna embedded in the capsule wall. The power induced in the coil by the magnetic field is fed to a tiny heater resistor located within a separate sealed electronics compartment inside the capsule. Although the power is only a few tenths of a wall, the small size of the heater (less than 1mm3) means that heat build up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This is turn, releases the spring and driver the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of

the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.

1.3.2.12. Multi particulates:

Multiparticulate (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time dependent and microbial control systems for colon targeting. Multiparticulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules.

A multi particulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (Eudragit S). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently controlled the release of budesonide, which is depended on the polymer concentration in the preparation. Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and (Asu1, 7) Eel calcitonin.

A multi particulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder. The drug reservoir was prepared by drug containing multi particulates like Non peariles in the

study. In this study the multi particulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery.

A Multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targeted delivery of metronidazole. The Multiparticulate system was prepared by coating cross-linked chitosan microspheres exploring Eudragit L-100 and S-100 as pH sensitive polymers. The in-vitro drug release studies shows that no release of drug at acidic pH and higher drug release were found in presence of rat caecal contents indicating susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents.

High-Amylose corn-starch and Pectin blend micro particles of diclofencac sodium for colon-targeted delivery were prepared by spray drying technique. The blending of high-amylose corn-starch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from pectin based micro particles. The drug released in colonic region by the action of pectinase from micro particles.

It was investigated that the effect of sodium glycocholate as absorption Promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger for colon-specific release, citric acid as a solubilizer of insulin, meglumine as a pH adjusting agent and sodium glycocholate as an absorption promoter.

1.4. Irritable bowel syndrome (IBS):

(**Spastic colon; Irritable colon; mucous colitis; Spastic colitis**)

(www.wikipedia.com)

Irritable bowel syndrome (IBS) is a disorder that leads to abdominal pain and cramping, changes in bowel movements, and other symptoms.IBS is not the same as inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis. In IBS, the structure of the bowel is not abnormal.

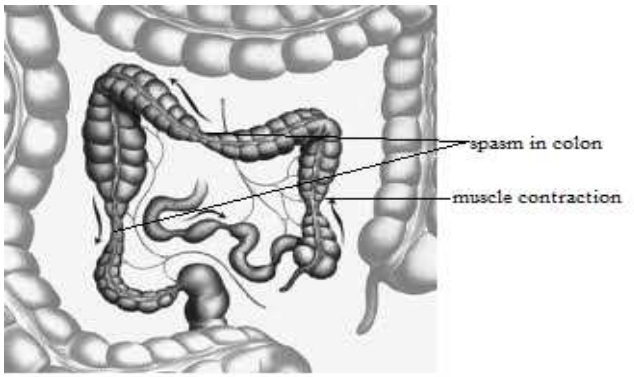


Fig.13: Showing muscle contraction of the large bowel in a case of irritable bowel syndrome.

Classification:

IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or IBS with alternating stool pattern (IBS-A or pain-predominant). In some individuals, IBS may have an acute onset and develop after an infectious illness characterized by two or more of the following: fever, vomiting, diarrhea, or positive stool culture. This post-infective syndrome has consequently been termed "post-infectious IBS" (IBS-PI)

- **Symptoms of IBS:**

The primary symptoms of IBS are abdominal pain or discomfort in association with frequent diarrhea or constipation, a change in bowel habits. There may also be urgency for bowel movements, a feeling of incomplete evacuation (tenesmus), bloating or abdominal distention. In some cases, the symptoms are relieved by bowel movements. People with IBS, more commonly than others, have gastro esophageal reflux, symptoms relating to the genitourinary system, chronic fatigue, fibromyalgia, headache, backache and psychiatric symptoms such as depression and anxiety. Some studies indicate that up to 60% of persons with IBS also have a psychological disorder, typically anxiety or depression.

- **Treatment and Medications for IBS:**
  - **Medications**

Medications may consist of stool softeners and laxatives in constipation-predominant IBS, and antidiarrheals (e.g., opiate, opioid, or opioid analogs such as loperamide, codeine, diphenoxylate) in diarrhea-predominant IBS for mild symptoms and stronger opiates such as morphine and oxycodone for severe cases. Drugs affecting serotonin (5-HT) in the intestines can help reduce symptoms. Serotonins stimulate the gut motility and so agonists can help constipation-predominate irritable bowel, while antagonists can help diarrhea-predominant irritable bowel.

- **Laxatives:**

For patients who do not adequately respond to dietary fiber, osmotic laxatives such as polyethylene glycol, sorbitol, and lactulose can help avoid "cathartic colon" which has been associated with stimulant laxatives. Among the osmotic laxatives, 17–26 grams/day of polyethylene glycol (PEG) has been well studied.

Lubiprostone (Amitiza) is a gastrointestinal agent used for the treatment of idiopathic chronic constipation and constipation-predominant IBS. It is well tolerated in adults, including elderly patients. As of July 20, 2006, Lubiprostone had not been studied in pediatric patients. Lubiprostone is a bicyclic fatty acid (prostaglandin E1 derivative) that acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements (SBM). Unlike many laxative products, Lubiprostone does not show signs of tolerance, dependency, or altered serum electrolyte concentration.

- **Antispasmodics:**

These of antispasmodic drugs (e.g., anticholinergics such as hyoscyamine or dicyclomine) may help patients, especially those with cramps or diarrhea. A meta-analysis by the Cochrane Collaboration concludes that if seven patients are treated with antispasmodics, one patient will benefit. Antispasmodics can be divided in two groups: neurotropics and musculotropics.

- Neurotropics, such as a phenobarbital like Donnatal or atropine, act at the nerve fibre of the parasympathicus but also affect other nerves and have side effects.

- Musculotropics such as mebeverine act directly at the smooth muscle of the gastrointestinal tract, relieving spasm without affecting normal gut motility. Since this action is not mediated by the autonomic nervous system, the usual anticholinergic side effects are absent.

CLASSIFICATION OF ANTISPASMODICS

Antimuscarinics (Anti-cholinergic):

1. Dicyclomine
2. Atropine
3. Hyoscine
4. Propantheline

Mebeverine and related compounds:

Alverine, Drotaverine, Penavarium

- **Tricyclic antidepressants:**

There is strong evidence that low doses of tricyclic antidepressants can be effective for irritable bowel syndrome. However, there is less robust evidence as to the effectiveness of other antidepressant classes such as SSRIs (Selective serotonin reuptake inhibitors).

1.5. Pelletization: *(www.pharmainfo.net)*

Pellets: Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral Administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. 1. Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm.

3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

4. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm.

5. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

6. Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

1.6. Significance of Pellets:

Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface & the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch.

Highlighted below are some of the few instances where smooth surfaced uniform pellets are being successfully used:

1. Improved appearance of the products. Coating of pellets can be done with different drugs to enable a controlled releaserate.

2. In case of immediate Release Products larger surface area of pellets enables better distribution.

3. Chemically incompatible products can be formed into pellets & delivered in a single dose byencapsulatingthem.

4. In the chemical industries it is used to avoid powder dusting.

5. Pellets ensure improved flow properties, and flexibility in formulation development and manufacture.

6. Coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having few coats.

1.7. Theory of pellet formation:

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

1.8. Methods of Preparing Pellets:

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

1.8.1. Powder layering:

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders,

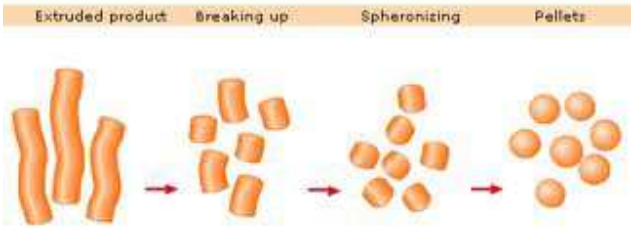
hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

1.8.2. Solution / suspension layering:

Solution/suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter/non-pareil seeds, which is an inert material or crystals/granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

1.8.3. Pelletization by Extrusion and Speronzation:

The process involves first making of extrudes from the powder material and then converting extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc), beads as fine as 0.6mm can be made.



1.9. Other Pelletization Methods:

Other pelletization methods such as globulation, cryopelletization, balling and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

Globulation or droplet formation consist two related processes, **spray drying** and **spray congealing.**

Spray drying:

It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs.

Spray congealing:

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce

spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

Cryopelletization:

It is a process in which the liquid formulation is converted in to solid spherical particles or pellets in the presence of liquid nitrogen as fixing medium. The shape depends up on the distance the droplet travel before contacting liquid nitrogen.

Compression:

It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

Balling:

It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid.

1.10. Enteric coatings:

Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intension is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.

Cracking of the film either during application or on storage will result in a loss of enteric properties. Therefore, consideration must be given to the mechanical properties of the applied film. Cracking problems can be effectively overcome by plasticization. Plasticizer can also be used to reduce the permeability of the polymer films to water vapor. The choice of suitable Plasticizer is restricted to non-water soluble materials because these are likely to be most effective.

An evaluation is made of the solubility parameters of species together with an assessment of the intrinsic viscosity of dilute solutions of the polymer on the plasticizers. This determines the maximum interaction between polymer and Plasticizer, and indicates which Plasticizer is likely to be most effective.

Important reasons for enteric coating are as follows:

-To protect acid-liable drugs from the gastric fluid

- to protect gastric distress or nausea due to irritation from drug

- To deliver drugs intended for local action in the intestines.

- To deliver drug that are optimally absorbed in the small intestine to their primary

absorption site in their most concentrated form.

-To provide a delayed release component to repeat actions.

-Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media (E.g. Esomeprazole, omeprazole, pantaprazole)

Enteric coating materials:

Enteric coatings work because they are selectively insoluble substances they won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine.

Most enteric coatings won't dissolve in solutions with a pH lower than 5.5. Commonly-used enteric coatings may be made from:

Methacrylic acid copolymers

Cellulose acetate (and its succinate and phthalate version)

Polymethacrylic acid/acrylic acid copolymer

Hydroxypropyl methyl cellulose phthalate

Poly vinyl acetate phthalate

Ethyl cellulose phthalate

Cellulose acetate tetra hydrophtalate

Acrylic resin

Shellac

The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.

Cellulose Acetate Phthalate (CAP):

Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

Poly Vinyl Acetate Phthalate (PVAP):

Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrates at pH 5

Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP):

It is available in two grades HP50 and HP55, HP55 solutions are more viscous than HP50, HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5.It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer.

Methacrylic acid copolymers:

Two grades are available A and B which differs in the ratio of free carboxyl to ester groups therefore:

Type A has a ratio of 1:1 and disintegrates at pH 6

Type B has a ratio of 1:2 and disintegrates at pH 7.

Available under the trade names Eudragit L and S correspond to NF types A & B.

1.11. Coating Equipments:

Most of the coating processes use one of three general types of equipments.

1. The standard Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

1.11.1. Conventional pan system:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface.

1.11.2. The Perforated Coating pan:

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 g to 1 kg. This model efficiently carries out the following operations: Aqueous film coating of tablets/pellets; Non-aqueous organic solvent based film coating of tablets/pellets; and enteric film coating of tablets/pellets.

The basic units of the system are: Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system

through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window.This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, ex-haust unit and an air fitter.

Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun, and inter-connecting flexible hoses.

1.11.3. The Fluidized bed coater:

The Fluid Bed Technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is as per GMP standards it is a closed system. The second advantage of the Fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine.

Fluidized bed coating is a process that takes place inside a fluidized bed whereby a coat is introduced to cover the intended object in order to protect it or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid Particles inside the bed. In the process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle. There is considerable diversity in methods of using fluidized bed technology. For e.g. liquids can be applied to fluidized particles in a variety of ways, including top, bottom and tangential spraying. For a given product, each method can offer markedly different finished product characteristics. Fluidized beds are used for coating because of their high

energy- and mass transfer. Fluidized beds for film coating can be divided into three groups

- Top-spray,
- Tangential-spray
- Bottom-spray equipment.

Top spray:

The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized The expansion chamber is conically shaped to allow uniform deceleration of air stream .The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization.This reduces egglomeration endencies.

The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle; this reduces droplet spray drying and provides for longer subsequent drying of the coated particles. The top spray coater has been used to apply aqueous and organic solvent based film coatings, controlled release coatings.

Bottom spray coating: (wurster process)

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition) with is raised slightly above the perforated plate, centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated plated is designed with large holes in the

area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the coating partition, and downward outside this partition. Material passing through coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state. Material circulates rapidly in this fashion and receives layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state material circulates rapidly in this fashion and receives a layer of coating on each pass through the coating partition. The ring of large holes on the periphery of perforated plate prevents the accumulation of material at the container wall.

Table 8: Parameters Used in Bottom Spray Equipment:

Inlet temperature	38-42ºC
Product temperature	32-36ºC
Exhaust temperature	32-38ºC
Spray rate	8-12mg/min
Peristaltic pump	12-18 rpm

LITERATURE SURVEY...

2. LITERATURE SURVEY

2.1. Literature Review:

Abdullah GZ., *et al.* (2010): Mebeverine HCl is a water soluble drug commonly used to treat irritable bowel syndrome by acting directly on the smooth muscles of the colon. This work was aimed at the formulation and in vitro evaluation of a colon-targeted drug delivery system containing mebeverine HCl. Matrix tablets were prepared using ethyl cellulose (EC), Eudragit RL 100 either solely or in Combination by wet granulation technique. Dissolution was carried out in 0.1 N HCl for 2h followedby pH 6.8 phosphate buffer for eight hours. Uncoated forms released more than 5% drug in 0.1 N HCl therefore, Eudragit L100 was used as a coat. The results indicated very slow release profile. As a result, single retardant was used to prepare the matrix and coated by Eudragit L 100. The matrix containing 7% Eudragit RL 100 and 6% of binder was subjected to further studies to assess the effect of different coats (Eudragit L 100-55 and cellulose acetate phthalate) and different binders (pectin and sodium alginate) on the release profile. Eudragit L 100 and pectin were the best coating agent and binder, respectively. The final formula was stable and it can be concluded that the prepared system has the potential to deliver mebeverine HCl in vivo to the colon.

Zhongguo Zhong Yao Za Zhi (2006): Shuxiong micropellets were prepared by using a centrifugal granulator. The formulation composition and process factors were optimized investigated by adopting several indices such as size distribution, repose angle, bulk density and friability as indexes.

Prabakaran L., *et al.* (2006): The aim of the investigation is to improve the dissolution, wettability, and Micromeritic behavior of domperidone, a dopamine antagonist, used in the Treatment of nausea and vomiting. Micropelletization technique, a possible Approach for ensuring maximum dissolution with enhanced wettability, and uniform Pellet size almost spherical so as to achieve the smooth gastric transit of drug have been estimated. Micro pellets were prepared utilizing solvent diffusion Technique and all the process parameters such as solvent-non-solvent ratio, Stirring speed, temperature, and effect of aggregating agent on the micropellets. Formulations have been optimized. The addition of an aggregating agent (10%v/v of isopropyl alcohol) improved the uniform micropellets formation and the method was Reproducible. The micromeritic properties such as size distribution, surface Property (using Scalar-USB digital photomicroscope), pack ability, and flow ability of the formulated micropellets were characterized. Fourier transforms infrared Spectroscopy (FTIR) and Differential scanning calorimetric (DSC) analysis were performed to explain the results. Formulated micropellets showed clear and highly improved in vivo dissolution behavior, probably due to high wettability. The micro pelletized drug was stable at room temperature, 25 degrees C/60% relative humidity (RH), and 45 degrees C/70% RH, after 12 weeks.

Tayade PT., *et al.* (2004): Ibuprofen-gelatin micropellets were prepared by the cross-linking technique using formaldehyde. Spherical micropellets having an entrapment efficiency of 65% to 85% were obtained. The effect of core to coat ratio, speed of agitation, temperature, and volume of oil phase was studied with respect to entrapment efficiency, micro pellet size, and surface characteristics. Fourier transform infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any

drug-polymer interaction. X-ray diffraction patterns showed that there is a decrease in crystallinity of the drug. The micromeritic properties of micropellets were found to be slightly changed by changing various processing parameters to give micropellets of good flow property. The in vitro release profile could be altered significantly by changing various processing parameters to give a controlled release of drug from the micropellets. The stability studies of the drug-loaded micropellets showed that the drug was stable at storage conditions of room temperature, 37 degrees C, 25 degrees /60% relative humidity (RH) and 45 degrees /60% RH, for 12 weeks.

Mallick S., *et al.* (2002): Flurbiprofen loaded ethyl cellulose micropellets with different drug loading were prepared by a quasi-emulsion solvent diffusion technique. Encapsulation parameters of micropellets such as actual drug loading, drug encapsulation efficiency (DEE) and loss of coating polymer (LCP) were determined. Actual drug loading was increased with the increased initial drug loading whereas encapsulation efficiency decreased with the increase of actual drug loading. Invitro drug release profiles of these micropellets were evaluated in distilled water (DW) and also in phosphate buffer solution (PBS) to indicate pH dependency release rates. All the batches of micropellets released about 35-59% in DW and 89-97% in PBS during the period of 8 h and the burst effect of about 50-75% in the first 1.5 h was seen only in PBS. The mechanism of release kinetics was evaluated by fitting the release data to the zero order, first order, Higuchi, Baker-Lonsdale and Pappas equations and also to the differential forms of zero order, first order and Higuchi model. Adequate fitting of release data was found with first order, Higuchi and Pappas models and hence these models were selected for F-test statistics for ascertaining the mechanism of drug release. Higuchi model of drug release in DW and

PBS of all the formulations was ruled out due to its significantly different F-value with other models. Thus, mechanism of release of flurbiprofen from ethyl cellulose micropellets may be explained by the diffusional exponent model of Pappas et al. as ascertained by F-test statistics rather than the same, based on some other diffusional models even though they have shown good correlation.

Baidya S., *et al.* (1999): The objective of the present investigation was to prepare nitrofurantoin Micropellets coated with a combination of Eudragit RS 100 and Eudragit RL100 Taken in varying ratios to achieve a sustained nitrofurantoin serum and urinary level over a prolonged period of time without any side effect. The method adopted was phase separation coacervation induced by non-solvent addition. The physical nature of the coating film was improved by a protective colloid, polyisobutylene (0% to 3% w/w). The optimized formulations were extensively evaluated for particle size analysis, Scanning Electron Microscopy, stability studies and finally in vitro and in vivo release studies and their statistical evaluation and correlation.

Bedi S., *et al.* (1999): Nitrofurantoin, a synthetic bactericidal drug, was encapsulated with Eudragit RS 100 polymer by a coacervation phase separation technique using variable proportions of polyisobutylene (0% to 3%) as a protective colloid. The micropellets were evaluated by scanning electron microscopy (SEM), particle size distribution, wall thickness, and loss of wall polymer was determined. The *invitro* release experiments were carried out over the entire pH range of the Gastrointestinal tract, the data obtained from the dissolution profiles were compared in the light of different kinetic models and the regression coefficients were compared. The in vivo studies were

performed on female human volunteers. A linear correlation was obtained from in vitro-in vivo studies.

Roy S.*, et al.* (1989): A controlled-release dosage form was manufactured by dispersing ethyl cellulosesol in acetone into a medium of mineral oil. Dapsone was used as the model drug. The powdered drug was dispersed in the ethyl cellulose sol, and the formulation variables affecting the production of the discrete and spherical micropellets and their size distribution were investigated. The percentage of SPAN 80 in the formulation affected the yield and physical properties of the micropellets. The in vitro drug release followed first-order diffusion-controlled dissolution. More than 85% of the drug was released over 5 hr for all formulation batches, with delayed release over the drug dissolution profile.

Sahoo SK.*, et al.* (2008): In the present study aceclofenac-gelatine micropellets were prepared by the cross linking technique using glutaraldehyde as cross linking agent and characterized by X-ray diffractometry, DSC and SEM. The effect of drug: polymer ratio, temperature of oil phase, amount if glutaraldehyde and stirring time was studied with respect to entrapment efficiency, micro pellet size and drug release characteristics. Spherical micropellets having entrapment efficiency of 57% to 97% were obtained.DSC analysis conformed the obscene of drug –polymer interations.The micromeritic studies of micropellets show improved flow property. The entrapment efficiency, micro pellet size and drug release profile was altered significantly by changing various processing parameters.

Simratha bedi.*, et al.* (1999): The purpose of this study was to design to evaluate a drug delivery system of nitrofurantoin to control urinary tract infections by achieving a

sustained nitrofurantoin serum and urinary level over a prolonged period of time but without the concomitant side effects. Ethyl cellulose multiparticulate micropellets containing nitrofurantoin were prepared by using emulsification /solvent evaporation technique. The optimized formulation were extensively evaluated using I.R. Spectroscopy, particle size analysis, SEM, stability studies and finally invitro and invivo release rate studies. No drug polymer interaction could be detected. The release of drug more or less followed zero order, first order higuchi and binominal model equation. The invitro release studies were monitored over the entire pHrange of GIT fluid. A linear correlation was obtained in the in vitro-in vivo studies.

Mandal M., *et al.* (1997): Micropellets of pentazocine hydrochloride were fabricated by the emulsion solvent evaporation method using different combinations of ethyl cellulose and Eudragit RL100. The polymer combinations, drug load, and pHof the dissolution medium were found to extert important effects on drug release profile. Release kinetics also showed a heterogeneous pattern.

Laila Fatima, *et al.* (2006): To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/ or absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon. The review is aimed at understanding recent advancements made in multiparticulate system for colon specific delivery of medicaments.

Libo Yang, *et al.* (2002): The necessity and advantages of colon-specific drug delivery systems have been well recognized and documented. In the past, the primary approaches to obtain colon-specific delivery achieved limited success and included prodrugs, pH and time-depending systems, and microflora-activated systems.

Khan M.S., *et al*. (2010): The purpose of this research was to develop and evaluate multiparticulates of alginate and chitosan hydrogel beads exploiting pH sensitive property for colon-targeted delivery of theophylline. Alginate and chitosan beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S100. All formulations were evaluated for particle size, encapsulation efficiency, swellability and in vitro drug release. In vitrodissolution studies performed following pH progression method demonstrated that the drug release from coated beads depends on coat weights applied and pH of dissolution media. Mechanism of drug release was found to be swelling and erosion-dependent. The studies showed that formulated alginate and chitosan beads can be used effectively for the delivery of drug to colon and a coat weight of 20% weight gain was sufficient to impart an excellent gastro resistant property to the beads for effective release of drug at higher pH values.

Varshosza J., *et al*. (2009): The objective of this study was to develop piroxicam enteric coated pellets using nonpareil seeds by powder layering technique to minimize its gastrointestinal adverse effects. Inert seeds were prepared by incorporating sugar, Avicel PH 101 and lactose. The obtained cores were then treated by PVP 10 w/v % solution using centrifugal granulator (CF-granulator) and then coated with micronized piroxicam using HPMC solution (8% w/v) as binder. The piroxicam pellets were finally coated with different polymers (Eudragit L30D-55, Eudragit L100, Eudragit NE30D, Acryleze, or mixture of Eudragits L30D-55 and NE30D) and plasticizers (triethyl citrate and polyethylene glycol 6000). Results showed that Eudragit L30D-55 with 3% weight gain accompanied with TEC produced suitable enteric coated pellets.

Singh S.K., ***et al*** **(2009)*:*** Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today1. The study was undertaken with an aim to develop delayed release micropellets dosage form for Lansoprazole which is a benzimidazole anti ulcer agent and is one of the most widely used drugs for treating mild and severe ulcers. The approach of the present study was to make a comparative evaluation among these polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulation of micro pellets were prepared using the fluid bed coater (FBC) with the air pressure 2.0 bar and the spray rate 10-15ml/min. Temperature of bed is varied from 35°C to 50°C and inlet temperature is varied from 50°C to 70°C and the effect of various parameter were observed such as air pressure, inlet and outlet temperature of FBC, it is observed that at high pressure the pellets are breaking. For bed and inlet temperature it is observed that at low temperature lumps are occurring in the formulation and at 2.0 bar air pressure, inlet temperature 60°C and bed temperature of 40°C is reliable for solution flow rate 10-15ml/min. Concerning results of prototype preparation of Lansoprazole the micro pellets were prepared using HPMC E5 polymer as release retardant in three different concentration i.e. 40%, 50%, 60% with three different concentration 8%, 10%, 12% of NaOH and Acrycoat L30D solution was used for enteric coating. Formulated micro pellets showed delayed *in vitro* dissolution behavior, probably due to optimized concentration of polymer. The micro pellets drug was stable at room temperature, 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines, after 3 months.

2.2. DRUG PROFILE

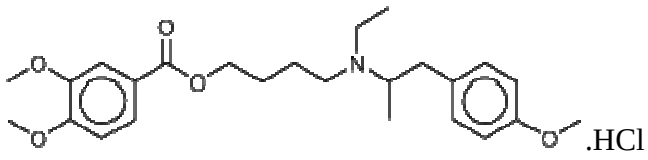
(Indian Pharmacopoeia, 2007*)*

(http://en.wikipedia.org/wiki/Mebeverinehttp://en.wikipedia.org/wiki/Colofac)

MEBEVERINE HYDROCHLORIDE

Mebeverine Hydrochloride is an anti-spasmodic drug given orally and topically (rectal route) for the treatment of irritable bowel disease. Mebeverine is also known as 4-(ethyl [1-(4-methoxyphenyl) propan-2-yl] amino) butyl 3, 4-dimethoxybenzoate.

Molecular structure:



Empirical formula : $C_{25}H_{35}NO_5$

Mol. Weight : 429.56 gm/mol

Category : Anti-spasmodic drug

CAS. No. : 2753-45-9

Physical state : White or Almost white crystalline powder

Melting point : 129-131˚C**.**

Odour : odorless or with a slight characteristic odour

Solubility : Freely soluble in ethanol (96%), very soluble in water, insoluble in ether.

Half life : The mean elimination half life is 2.5 hours.

Pharmacology: *(From Wikipedia, the free encyclopedia,)*

a. Mode of action:

Mebeverine is an anti muscarinic. Mebeverine belongs to a group of compounds called musculotropic antispasmodics. These compounds act directly on the gut muscles at the cellular level to relax them. Mebeverine is also an inhibitor of calcium-depot replenishment. Therefore, mebeverine has dual mode of action which normalizes the small bowel motility.

b. Pharmacokinetic parameter:

The plasma half-life of Mebeverine is reported to be about 2.5 hours; it is 60-75% bound to plasma proteins and peak plasma concentration will produce within 1-3hours.

c. Indications:

- Spastic functional disturbances of the colon
- Irritable bowel syndrome in its primary form, irritable bowel syndrome associated with organic lesions of the gastrointestinal tract such as; diverticulosis and diverticulitis, regional enteritis, disease of the gall bladder and gall ducts, gastric and duodenal ulcers, dysentery, and aspecific or specific inflammation of the digestive tract.
- Mebeverine should be taken 20 minutes before meals.

d. Uses:

Mebeverine is used to treat a number of problems.

- It is a direct relaxant of gut (intestinal) muscle, and is sometimes known as an antispasmodic drug.

- It is used to relax the muscles of the intestine and to treat symptoms of irritable bowel syndrome and related conditions.
- In general this drug is used to manage the symptoms of irritable bowelsyndrome, a common intestinal condition which causes spasm and pain in the intestine, aswellas stomachpain,persistent diarrhoea (sometimes alternating with periods of constipation) and wind (flatulence).
- Benefits of being on this drug include reducing the painful and troublesome symptoms of irritable bowel syndrome.

Listed below are the typical uses of mebeverine.

- Relief from the symptoms of irritable bowel syndrome as well as other conditions usually included in this grouping, such as chronic irritable colon, spastic constipation, mucous colitis and spastic colitis.
- On occasion your doctor may prescribe this medicine to treat a condition not on the above list. Such conditions are listed below.

e. Adverse Effects:

- reactions consisted of urticariaor maculopapular rash, sometimes accompanied by fever, polyarthritis, thrombopenia or angioedema

f. Contraindication:

Mebeverine is contraindicated in cases with

- Paralytic ileus (lack of bowel movements, leading to blockage of the gut).

- Any bleeding disorders (especially bleeding from the gut), severe constipation, having difficulty or pain when passing urine (water), recently had a fever, bloody stools, or have had abnormal vaginal bleeding or discharge.

Pregnancy

Mebeverine is suitable to take during pregnancy.

It is sensible to limit use of medication during pregnancy whenever possible. However, your doctor may decide that the benefits outweigh the risks in individual circumstances and after a careful assessment of your specific health situation.

Breast feeding

Mebeverine is suitable to take if you are breastfeeding.

It is sensible to limit use of medication during breastfeeding whenever possible.

Marketed Products Available:

- Mebeverine is presented in the United Kingdom as a (135 mg) tablet. Other strengths: 100 mg tablet and 200 mg capsule.
- It was first registered in 1965. It is manufactured and marketed as Colofac, Duspatal and Duspatalin by Solvay Pharmaceuticals.

2.3. POLYMERS AND EXCIPIENTS PROFILE:

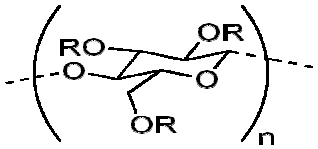
(Rowe R C, 4th edition)

2.3.1. HYDROXY PROPYL METHYL CELLULOSE

Synonyms: Benecel, HPMC, Methocel, Hydroxy propyl methyl cellulose

Molecular weight: 10,000-15,000

Structure:



R = H or CH_3 or $CH_2CH(OH)CH_3$

Description : slightly off-white to beige powder in appearance and may be formed into granules.

Colour : white to yellowish white

Odour : odorless or nearly odorless

Taste : bland taste

Texture : powder

Acidity / Alkalinity : pH 5.5-8.0 for a 1%w/w aqueous solution.

V**iscosity for 2 %(w/v) aqueous solution:** 4000mpas (Viscosity measured at 200C)

Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in mixtures of ethanol and dichloromethane, mixtures of alcohol and water

Functional category:

Coating agent, film former, and rate controlling polymer for sustained release, stabilizing agent, suspending agent and viscosity builder.

Applications in pharmaceutical technology:

High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80%w/w in tablets and capsules.

Stability and Storage:

Stable between pH 3-11, should be stored in a well-closed container in a cool and dry place.

Incompatibilities:

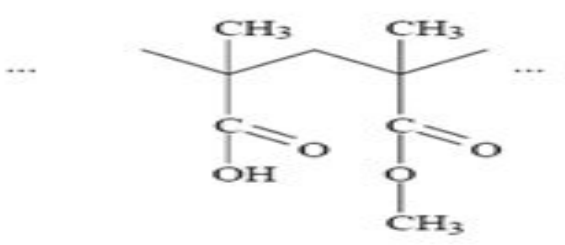
Incompatible with some oxidizing agents such as hydrogen peroxide, potassium permanganate.

2.3.2. EUDRAGIT S100

Synonyms : Methacrylic Acid-Methacrylate Copolymer (1:2).

C.A.S. No. : 25086 – 15 – 1

Structure :



Chemical/IUPAC name : Poly (methacylic acid-co-methyl methacrylate) 1:2

INCI name : Acrylates Copolymer

Description : White powders with a faint characteristic odour.

Solubility:

1gm of Eudragit S 100 dissolves in 7 g methanol, ethanol,in aqueous isopropyl alcohol ethanol, and acetone (containing approx.3% water),as well as in 1N NaOH to give clear to slight cloudy solution.

Film formation:

When the test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvent.

Characteristics:

- Granulation of drug substances in powder form for controlled release
- Effective and stable enteric coatings with a fast dissolution in the upper Bowel
- Site specific drug delivery in intestine by combination with Eudragit S grades
- Variable release profiles

Applications:

Eudragit is widely used in oral pharmaceutical formulations, especially in targeting drug delivery system in GIT. Eudragit is used to prepare sustained-release preparations.

Loss on Drying: Max. 5.0 % according to "Dry substance / Residue on evaporation."

Viscosity (dynamic): 50 - 200 mPas.

Stability and Storage:

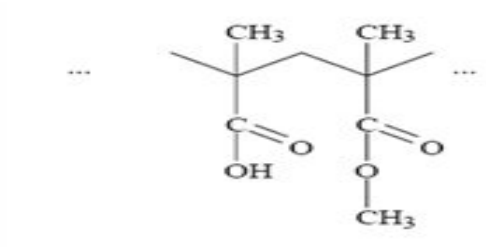
Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Protect from warm temperatures (USP, General Notices). Protect against moisture

2.3.2. EUDRAGIT L100

Synonyms : Methacrylic Acid-Methacrylate Copolymer (1:1).

C.A.S. No. : 25086 – 15 – 1

Structure :



Chemical/IUPAC name : Poly (methacylic acid-co-methyl methacrylate) 1:1

INCI name : Acrylates Copolymer

Description : White powders with a faint characteristic odour.

Solubility:

1gm of Eudragit L 100 dissolves in 7 g methanol, ethanol,in aqueous isopropyl alcohol and acetone (containing approx.3% water),as well as in 1N NAOH to give clear to slight cloudy solution.

Film formation:

When the test solution is poured onto a glass plate, a clear film forms upon evaporation of the Solvent.

Characteristics:

- Granulation of drug substances in powder form for controlled release
- Effective and stable enteric coatings with a fast dissolution in the upper Bowel
- Site specific drug delivery in intestine by combination with Eudragit S grades
- Variable release profiles

Applications:

Eudragit is widely used in oral pharmaceutical formulations, especially in targeting drug delivery system in GIT. Eudragit is used to prepare sustained-release preparations.

Loss on Drying: Max. 5.0 % according to "Dry substance / Residue on evaporation."

Viscosity (dynamic): 50 - 200 mPas.

Stability and Storage:

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Protect from warm temperatures (USP, General Notices). Protect against moisture

AIM & OBJECTIVES....

3. AIM AND OBJECTIVES

Mebeverine Hydrocloride is used an anti-spasmodic agent mainly used in treatment of IBD's(Irritable bowl disease).Mebeverine is the most active and exceptionally safe anti-inflammatory action as compared to any other NSAID in its class. Therefore Mebeverine hydrocloride was selected to carry out present work which is aimed to develop colon targeted micro pellets prepared by for treatment of IBD's. In order to treat the colonic diseases more effectively than conventional delivery systems, such a drug delivery system is required which will be able to target the drug to diseased colon. The colon specific drug delivery has achieved the most important because the colon is an area that is vulnerable to a no.of disease including ulcerative disease, crohn's disease, IBD's and carcinomas. Treatment of this disease with colonic specific drug delivery system provides an interesting alternative over systemic drug administration because of lower dosing and fewer systemic side effects. Colon targeted drug delivery system (colon targeted micro pellets) inhibits drug release in stomach and small intestine and releases most of the drug into colonic region. Thus availability of drug at targeted site will be near to 100%.

To improve the site specificity of pH dependent systems (because of large variation in pH of GIT) and variable results with time dependent systems (variation in the gastric emptying time and small intestine transit time) led to development of alternative approaches for colon specific drug delivery based on various carriers (that are being

degraded by colonic bacterial action) like pectin and its salts, chondrotin sulphate, amylose, inulin HP, and guar gum etc.

The present project is based on to develop a novel micro pellets prepared by powder layering technique being the most widely used today. The study was under taken with aim to develop colon targeted micro pellets dosage form for mebeverine hydrochloride.

❖ Objectives:

The objective of the present study is preparing the micropellets of mebeverine hydrochloride in order to provide controlled release and colon targeting. The micro pellets of mebeverine hydrochloride were formulated by powder layering technique and further coating with eudragit L100 and eudragit S100.The micro pellets is evaluated with respect to particle size, drug content, entrapment efficiency and loose surface crystal study. Drug polymer compatibility studied by FTIR and DSC. In-vitro drug release study, release kinetics studies and stability studies.

PLAN OF WORK....

4. PLAN OF WORK

- **Literature survey**.
- **Materials and equipments.**
- **Preformulation studies.**
  - **Characterization of Drug.**
    - Appearance.
    - Melting Point Determination.
    - Solubility Study.
    - UV Spectroscopy (λ_{max}).
    - IR Spectroscopy.
    - Loss on drying.
  - **Drug - Polymers Interaction Studies.**
    - Fourier transforms Infra-Red (FTIR) Spectroscopy Study.
    - Differential Scanning Calorimetry (DSC) Analysis.
  - **Preparation of Mebeverine hydrochloride micropellets.**
  - **Evaluation of Mebeverine hydrochloride micropellets.**
    - Appearance.
    - Particle size.
    - Micromeritic properties for micropellets.
    - Evaluation of micropellets.
    - Content uniformity.

- Loose surface crystal studies.
- Loss on drying.
- Scanning electron microscopy.
- Invitro drug release studies.
- Release drug data model fitting.

- **Results and Discussion.**
- **Summary and Conclusion.**
- **Future Prospects.**
- **Bibliography.**

MATERIALS & EQUIPMENTS....

5. MATERIALS AND EQUIPMENTS

5.1. List of Materials used with Sources

Table 9: List of Materials and their Suppliers

S. No.	Name of Material	Supplied by
1	Mebeverine Hydrochloride	Bindu pharmaceuticals, Hyderabad.
2	PVP K30	Richer health care, Hyderabad.
3	Lactose pellets	Bindu pharmaceuticals, Hyderabad.
4	HPMC K4m	Richer health care, Hyderabad.
5	Eudragit L100	Richer health care, Hyderabad.
6	Eudragit S100	Richer health care, Hyderabad.
7	Iso propyl alcohol	Richer health care, Hyderabad.
8	Water	Richer health care, Hyderabad.

5.2. List of Equipments used with model:

Table 10 : List of equipments with their make

S. No.	Name of the equipment	Make
1	Electronic balance	Shimadzu, Japan
2	UV-Visible spectrophotometer	Shimadzu, Japan
3	Standared coating pan	Ganson-india
4	FTIR Spectrophotometer	Shimadzu
5	DSC test apparatus	Mettler Teldo
6	Dissolution test apparatus	Vigo Scientifics, Mumbai
7	Digital pH meter	Elico Scientifics, Mumbai
8	Hot air oven	Precision scientific co., Chennai
9	Humidity chamber	Lab tech, Ambala
10	Tap density apparatus	Indo labs, Chennai
11	Melting point test apparatus	Precision scientific co., Chennai
12	Optical microscope	Mettler Toledo
13	SEM	Merlin-FE-SEM

PRE-FORMULATION STUDIES....

6. PRE-FORMULATION STUDIES

6.1. Characterization of Drug:

6.1.1. Colour and Appearance: *(Indian Pharmacopoeia, 2007)*

The sample was observed visually.

6.1.2. Melting Point: *(Indian Pharmacopoeia, 2007)*

Melting point of drug was determined by Melting point test apparatus.

6.1.3. Solubility: *(Indian Pharmacopoeia, 2007)*

Solubility study was carried out as per the I.P.2007.In this maximum amount of solvent required to dissolve the solute was determined.

6.1.4. Spectral Analysis of Mebeverine Hydrochloride:

(Indian Pharmacopoeia, 2007; Zayed S.I.M, 2005)

6.1.4.1. UV Spectral Analysis of Mebeverine:

6.1.4.1.1. UV Spectral Analysis of Mebeverine in methanol:

6.1.4.1.1.1. Determination of absorption maximum in methanol:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in methanol and final volume was made to100 ml. A dilution of (25 µg/ml) was kept in cuvette. The solution was scanned in the range of wavelength 200 – 400 nm. The UV spectrum showing λmax was recorded using double beam UV-Visible spectrophotometer

6.1.4.1.1.2. Preparation of Standard Curve of Mebeverine in methanol:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in methanol and final volume was made to 100 ml. The solutions in concentration range of 5-25 µg/ml were prepared by appropriate dilutions of stock solution. The UV

absorbances of these solutions were determined spectrophotometrically at λmax 263 nm using double beam UV-Visible spectrophotometer.

6.1.4.1.2. UV Spectral Analysis of Mebeverine by using 0.1N HCl:

6.1.4.1.2.1. Determination of absorption maximum in 0.1N HCl:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in 0.1N HCl and final volume was made to 100 ml. A dilution of 25 µg/ml was kept in cuvette. The solution was scanned in the range of wavelength 200 – 400 nm. The UV spectrum showing λmax was recorded using double beam UV-Visible spectrophotometer.

6.1.4.1.2.2. Preparation of Standard Curve of Mebeverineine in 0.1N HCl:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in 0.1N HCl and final volume was made to 100 ml. The solutions in concentration range of 5 -25 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbances of these solutions were determined spectrophotometrically at λmax 263.4 nm using double beam UV-Visible spectrophotometer.

6.1.4.1.3. UV Spectral Analysis of Mebeverine by using Phosphate buffer pH 6.8:

6.1.4.1.3.1. Determination of absorption maximum in Phosphate buffer pH 6.8:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in Phosphate buffer pH 6.8 and final volume was made to 100 ml. A dilution of 25 µg/ml was kept in cuvette. The solution was scanned in the range of wavelength 200 - 400 nm. The UV spectrum showing λmax was recorded using double beam UV-Visible spectrophotometer.

6.1.4.1.3.2. Preparation of Standard Curve of Mebeverine in Phosphate buffer pH 6.8:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in Phosphate buffer pH 6.8 and final volume was made to 100 ml. The solutions in concentration range of 5 - 25 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbances of these solutions were determined spectrophotometrically at λmax 263 nm using double beam UV-Visible spectrophotometer.

6.1.4.1.4. UV Spectral Analysis of Mebeverine by using Phosphate buffer pH 7.4:

6.1.4.1.4.1. Determination of absorption maximum in Phosphate buffer pH 7.4:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in Phosphate buffer pH 6.8 and final volume was made to 100 ml. A dilution of (25 µg/ml) was kept in cuvette. The solution was scanned in the range of wavelength 200 – 400 nm. The UV spectrum showing λmax was recorded using double beam UV-Visible spectrophotometer.

6.1.4.1.4.2. Preparation of Standard Curve of Mebeverine in Phosphate buffer pH 7.4:

A stock solution of Mebeverine (100 µg/ml) was prepared by dissolving 10 mg of drug in Phosphate buffer pH 7.4 and final volume was made to 100 ml. The solutions in concentration range of (5 -25 µg/ml) were prepared by appropriate dilutions of stock solution. The UV absorbances of these solutions were determined spectrophotometrically at λmax 263 nm using double beam UV-Visible spectrophotometer.

6.1.5. Infrared Spectrum: *(Robert M. Silverstein, 2003)*

The infrared spectrum of Mebeverine was recorded by using FTIR (Perkin elmer-Pharmaspec-1) instrument. A small quantity of sample was mixed with equal quantity of potassium bromide and placed in sample cell to record its IR spectra.

6.1.6. Loss on drying: *(Indian Pharmacopoeia, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

6.2. Drug - polymers compatability studies:

Drug polymers studies holds great importance in designing a formulation In drug formulation it is essential to evaluate the possible interactions between the active principle and the polymers, as the choice of the polymers should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product.

6.2.1. Fourier Transform Infra-Red Spectroscopy (FTIR) Study:

(Robert M. Silverstein, 2003; Becket A. H., 2005)

Mebeverine powder was mixed with various polymers in the ratio of 1:1. Then, the samples were scanned with FTIR (Perkin Elmer-Pharmaspec-1) over a wave number range of 4000-400 cm^{-1}.

6.2.2. Differential Scanning Calorimetry Study (DSC): *(Jain N. K., 2008)*

Mebeverine powder was mixed with various polymers in the ratio of 1:1.The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (10^0C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with polymers? Thermo grams of pure drug are used as a reference.

Appearance or disappearance of one or more peaks in thermo grams of drug with polymer are considered as an indication of interaction.

FORMULATION OF MICROPELLETS....

7. FORMULATION OF MICROPELLETS

Table 11: Composition of Colon Targeted Micropellets of Mebeverine hydrochloride:

S. No.	Ingredients (mg/capsule)	Formulations Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Mebeverine HCl**	20	20	20	20	20	20	20	20	20
2	**PVP K30**	6	6	6	6	6	6	6	6	6
3	**Lactose pellets**	160	150	140	160	150	140	140	150	160
4	**HPMC K4M**	6	8	10	6	8	10	10	8	6
5	**Eudragit S100**	8	16	24	-	-	-	12	8	4
6	**Eudragit L100**	-	-	-	8	16	24	12	8	4
7	**Isopropyl alcohol**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	**Water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total fill weight	200	200	200	200	200	200	200	200	200

Coating of pellets:

There are three stages in coating of micro pellets

- Drug loading.
- Drying.
- Sub coating with polymers.

Preparation of mebeverine HCl micropellets:

The micropellets of Mebeverine hydrochloride were prepared by pan coating powder layering technique. The formulation of delayed release micropellets of mebeverine hydrochloride were done by using polymers HPMC K4M, Eudragit L100, Eudragit S100.

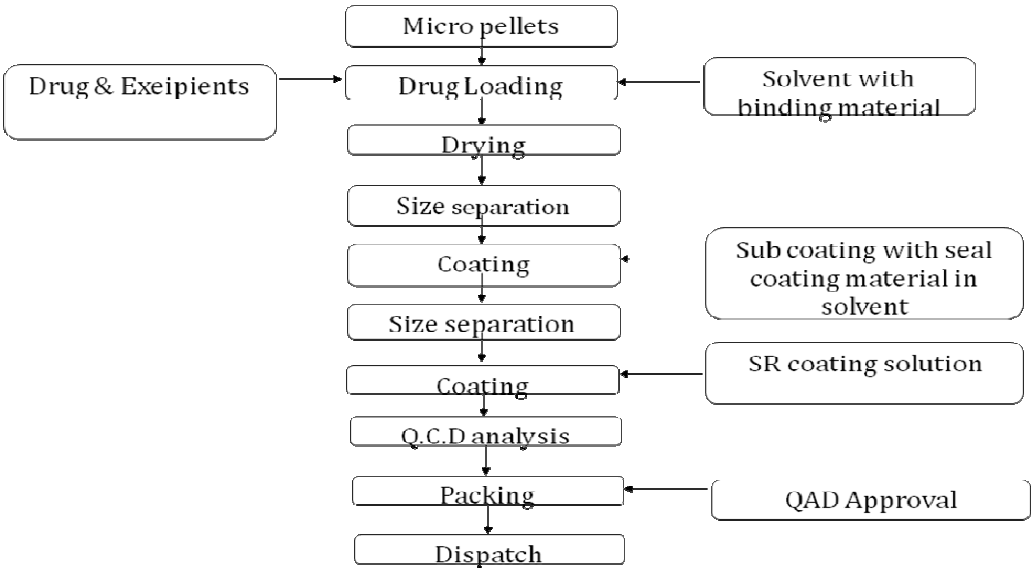
Drug Loading:

Lactose pellets were sieved through 30#40 sieves and pellets was taken for drug loading from total batch size, required quantity of drug was taken and dispersed in binder solution stirred for 10min and pellets were loaded with drug by coating of drug with binder solution. The drug loaded micropellets were dried at 45^0 C for 8 hours in stainless steel tray drier. Check moisture content, it should be below 1%. Then pass the pellets through sifters to remove fines.

Coating with polymers:

Drug loaded micropellets were coated with coating polymers(HPMC K4M, Eudragit L100, Eudragit S100)in different ratios. Spay the coating solution through nozzle on pellets along with continuous flow of warm air in, to dry the coat as soon as it forms uniform coating.

Preparation of micropellets by powder layering



EVALUATION OF MICROPELLETS....

8. EVALUATION OF MICROPELLETS

- **Evaluation of Micropellets:**
  - **Micromeritic Properties of Micropellets.**
    - Appearance.
    - Particle size.
    - Angle of repose.
    - Bulk density.
    - Tapped density.
    - Carr's index.
    - Hausner's ratio.
  - **Evaluation of Micropellets.**
    - Drug content.
    - Loose surface crystal study.
    - Loss on drying.
    - Scanning electron microscopy.
  - ***In-vitro* drug release studies.**
  - **Release drug data model fitting.**
  - **Stability Studies.**

8.1. MICROMERITIC PROPERTIES OF MICROPELLETS:

8.1.1. Appearance:

The pellets were visually observed for physical appearance of pellets.

8.1.2. Particle size: *(Choudhury P.K et al,2010)*

Particle size distribution of micropellets was determined by optical microscopy using calibrated ocular eye piece. Fifty micropellets were evaluated and the experiment was performed. Geometric mean diameter was then calculated using the equation.

$Xg=10 X [(n_i X \log X_i)/N]$

X_g is geometric mean diameter, n_i is number of particles in the range, X_i is the midpoint of range, N is total number of particles analyzed.

8.1.3. Angle of repose:

The dried micropellets were allowed to fall freely through a funnel fixed at 1 cm on a horizontal surface and the angle of repose (θ) was measured.

$\theta = \tan^{-1} h/r.$

Where h is the height of the heap, r is the radius.

8.1.4. Bulk density and tapped density:

An accurately weighed (10 gm) pellets from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the pellets was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped

volume. Both Bulk Density (BD) and Tapped Bulk Density (TBD) of pellets were determined using the following formulae.

BD = Weight of the pellets/Volume of the pellets

TBD = Weight of the pellets/Tapped volume of the pellets

8.1.5. Carr's Compressibility Index:

The compressibility index of the pellets was determined using following Carr's compressibility index formula.

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flow ability is shown in the Table 12.

Table 12: Relationship between % Compressibility and Flow ability

S. No.	% Compressibility	Flow ability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

8.1.6. Hausner's ratio:

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Table 13: Relationship between Hausner's ratio and Flow ability

S. No.	Hausner's ratio	Flow Property
1	0.0 - 1.25	Free flow
2	1.25 - 1.6	Cohesive flow

8.2.EVALUATION OF MICROPELLETS: *(choudhury P.K et al, 2010)*

8.2.1. Drug Content:

200mg pellets were weighed and powdered, a quantity of powder equivalent to 20 mg of each formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 263 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

8.2.2. Loose surface crystal study: *(choudhury P.K et al, 2010)*

About 200 mg of micropellets were accurately weighed and suspended in phosphate buffer pH6.8. They were shaken vigorously for 5 min. The leaked out solution is analyzed spectrophotometrically at 263 nm.

8.2.3. Loss on drying:

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

8.2.4. Scanning electron microscopy:

Morphological examination of the surface and internal structure of the dried beads was performed by using a scanning electron microscope (SEM). Micropellets before dissolution only subjected to SEM study since, after dissolution the pellets become swollen palpable mass. Photographs were taken within the range of 50-500 magnification.

8.3. *INVITRO* DRUG RELEASE STUDIES:

8.3.1. Drug release studies in 0.1 N HCl: *(Khan M.S et al, 2010; Gang cheng et al.)*

Drug release studies were carried out by using USP dissolution type II test apparatus. The pellets were tested for drug release for 2 hours in 0.1N HCl (900ml) as the average gastric emptying time is about 2 hours. 5ml of samples were withdrawn at the interval of 1 hour and diluted up to 10 ml with 0.1N HCl. The absorbances were measured at 263 nm. Using a double beam UV spectrophotometer to find out the amount of Mebeverine released from Micropellets.

8.3.2. Drug release studies in pH 6.8 phosphate buffer*:*

(*Khan M.S et al, 2010; Tereza Bautzová et al, 2011)*

After drug release studies carried out in 0.1 N HCl, the dissolution medium was replaced by pH 6.8 phosphate buffer (900ml) and tested for drug release for 3 hours as

the average small intestinal transit time is about 3 hours. 5ml of samples were withdrawn at the interval of 1 hour and diluted up to 10 ml with pH 6.8 phosphate buffer. The absorbance was measured at 263 nm, using a double beam UV spectrophotometer to find out the amount of Mebeverine released from Micropellets.

8.3.3. Drug release studies in pH 7.4 phosphate buffer:

After drug release studies carried out in pH 6.8 phosphate buffer, the dissolution medium was replaced by pH 7.4 phosphate buffer (900ml) and tested for drug release for 3 hours as the average small intestinal transit time is about 5-12 hours. 5ml of samples were withdrawn at the interval of 1 hour and diluted up to 10 ml with pH 7.4 phosphate buffer. The absorbance was measured at 263 nm, using a double beam UV spectrophotometer to find out the amount of Mebeverine released from Micropellets.

Table14. Parameters for *In Vitro* Drug Release

1	Apparatus	USP type II apparatus (Paddle type)
2	Temperature	37 ± 0.5° C
3	Initial Volume	900ml
4	Speed	100 rpm
5	Drawn volume	5 ml
6	Running time	2 hrs in 0.1N HCl, 3 hrs in phosphate buffer pH 6.8 and 7 hrs in phosphate buffer pH 7.4.
7	Medium Replacement	Media refilling at 2 hrs and 5hrs

8.4. RELEASE DRUG DATA MODEL FITTING: *(Choudhury P.K et al, 2010)*

The suitability of several equation that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the release data up to the first 50% drug release. The data were evaluated according to the following equations.

Zero order model.

$$Mt = M_0 + K_0 t$$

Higuchi model.

$$Mt = M_0 + K_H t^{0.5}$$

Korsmeyer-peppas model.

$$Mt = M_0 + K_k t^n$$

Where Mt is the amount of the drug dissolved in time t. M_0 is the initial amount of drug. K_0 is the Zero order release constant, K_H is the Higuchi rate constant, K_K is a release constant and n is the release exponent that characterizes the mechanism of drug release.

8.5. STABILITY STUDIES: *(Janes T., 2000, Singh S.K et al,2009)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled “Stability testing

of New Drug Substances and Products" describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

Stability studies were carried out at 40°C / 75% RH for the optimized formulation for 3 months. The micropellets were stored at 40°C/75% RH as per ICH guidelines and various parameters(drug content and drug release profile) were monitored periodically for 3 months.

RESULTS & DISCUSSION....

9. RESULTS AND DISCUSSION

9.1. CHARACTERIZATION OF DRUG:

9.1.1. Colour and Appearance:

The drug (Mebeverine HCl) colour is "White or off white Powder" as same as the reported reference.

9.1.2. Melting Point:

The Melting point of Mebeverine HCl was found to be 130.5°C. The reported melting point of Mebeverine is 129°C-131°C. Hence, observed values are complies with IP.

9.1.3. Solubility Study:

The Solubility of Mebeverine HCl in different solvents is given below:

Table 15: Solubility of Mebeverine in Different Solvents

S. No.	Solvent	Parts of solvent required per part of solute	Inference
1	Distilled water	0.9	Very soluble.
2	Ethanol (95%)	7	Freely soluble.
3	0.1 N HCl	550	Slightly soluble.
5	Phosphate buffer pH 7.4	700	Slightly soluble.
6	Phosphate buffer pH 6.8	900	Slightly soluble.

9.1.4. SPECTROSCOPIC STUDIES:

9.1.4.1. UV Spectroscopy:

9.1.4.1.1. Determination of λmax and Preparation of Calibration Curve of Mebeverine by using methanol:

UV absorption spectrum of Mebeverine in methanol shows λmax at 263 nm. Absorbance obtained for various concentrations of Mebeverine in water are given in Table 16. The graph of absorbance concentration for Mebeverine was found to be linear in the concentration range of 5 – 25 µg /ml. The drug obeys Beer- Lambert's law in the range of 5 – 25 µg /ml.

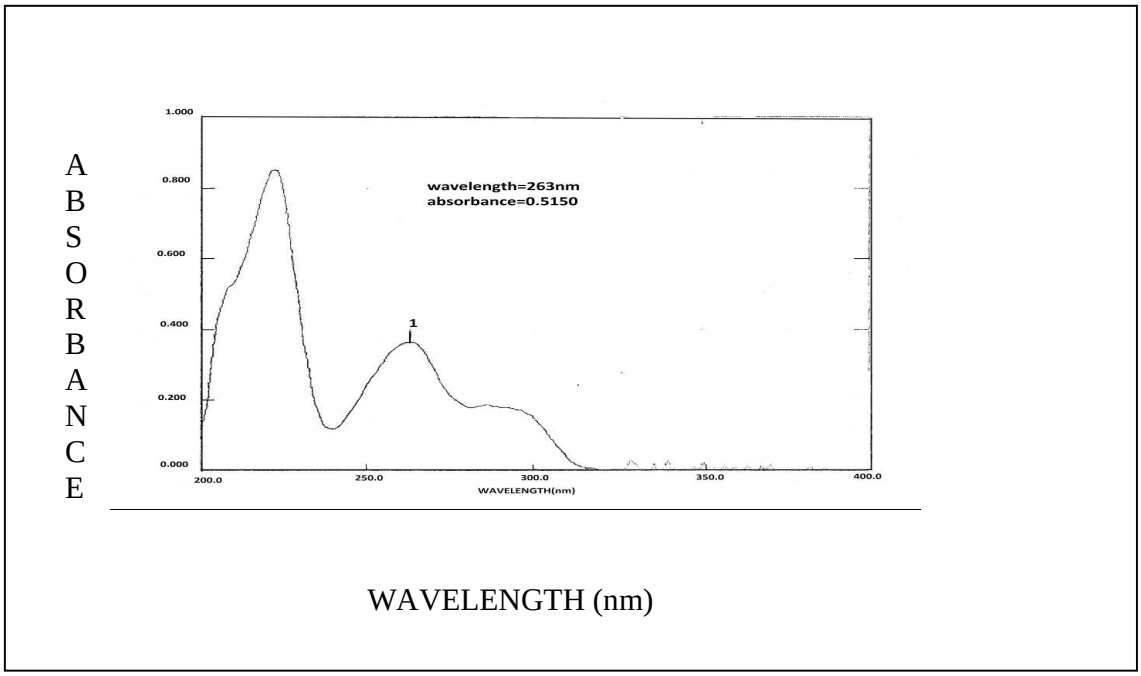


Fig. 14: Absorption maximum of Mebeverine in methanol

Table 16: Concentration and Absorbance data for Calibration Curve of Mebeverine in methanol

S. No.	Concentrations(µg/ml)	Absorbance at 263 nm
1	Blank	0
1	5	0.0920
2	10	0.1840
3	15	0.2761
4	20	0.3680
5	25	0.5150

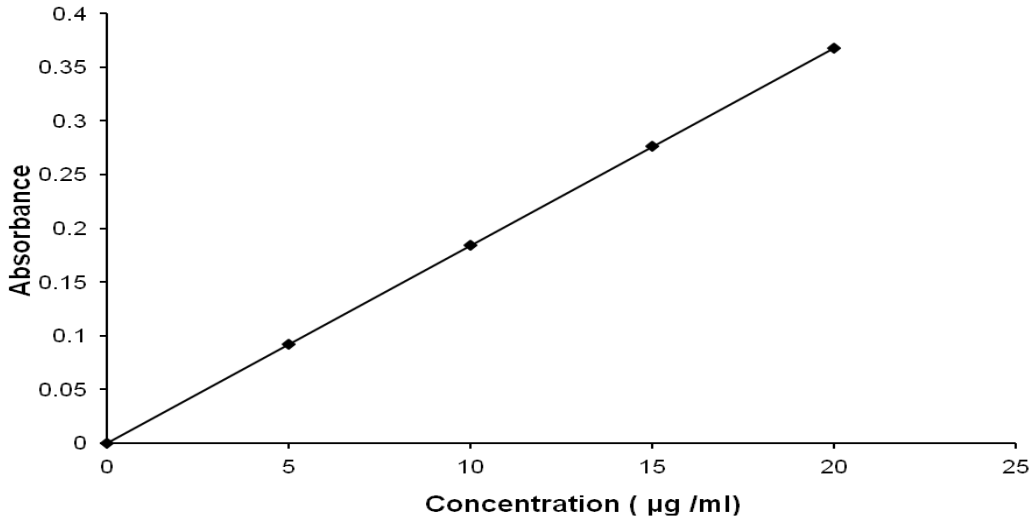


Fig. 15: Calibration Curve of Mebeverine in methanol

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 17.

Table 17: Data for Calibration Curve parameters of Mebeverine in methanol

S. No.	Parameters	Values
1	Slope	0.0184
2	Intercept	0.0219
3	Correlation coefficient (R)	0.9989

9.1.4.1.2. Determination of λmax and Preparation of Calibration Curve of Mebeverine by using 0.1N HCl

UV absorption spectrum of Mebeverine in 0.1N HCl shows λmax at 263.4 nm. Absorbance obtained for various concentrations of Mebeverine in 0.1N HCl are given in Table 18. The graph of absorbance versus concentration for Mebeverine was found to be linear in the concentration range of 5 – 25 µg /ml. The drug obeys Beer- Lambert's law in the range of 5– 25 µg /ml.

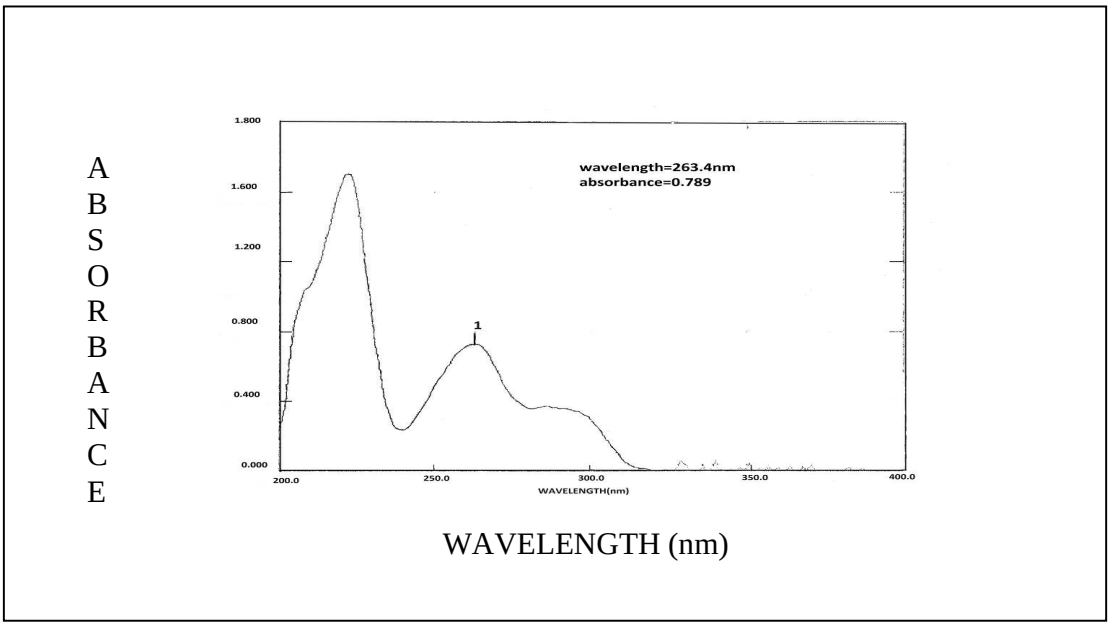


Fig. 16: Absorption maximum of Mebeverine in 0.1N HCl

Table 18: Concentration and Absorbance data for Calibration Curve of Mebeverine in 0.1N HCl

S. No.	Concentrations (µg/ml)	Absorbance at 263.4nm
1	Blank	0
2	5	0.166
3	10	0.329
4	15	0.488
5	20	0.632
6	25	0.789

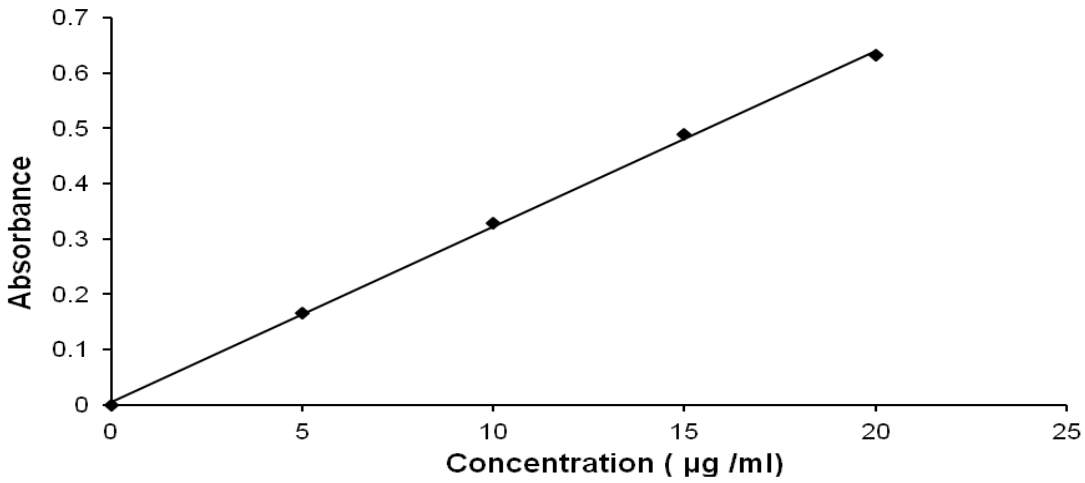


Fig. 17: Calibration curve of Mebeverine in 0.1N HCl

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 19.

Table 19: Data for Calibration Curve parameters of Mebeverine in 0.1N HCl

S. No.	Parameters	Values
1	Slope	0.0317
2	Intercept	0.0058
3	Correlation coefficient (R)	0.9997

9.1.4.1.3. Determination of λmax and Preparation of Calibration Curve of Mebeverine by using Phosphate buffer pH 6.8:

UV absorption spectrum of Mebeverine in pH6.8 phosphate buffer shows λmax at 263 nm. Absorbance obtained for various concentrations of Mebeverine in Phosphate buffer pH 6.8 are given in Table 20. The graph of absorbance versus concentration for Mebeverine was found to be linear in the concentration range of 5 – 25 µg /ml. The drug obeys Beer- Lambert's law in the range of 5 – 25 µg /ml.

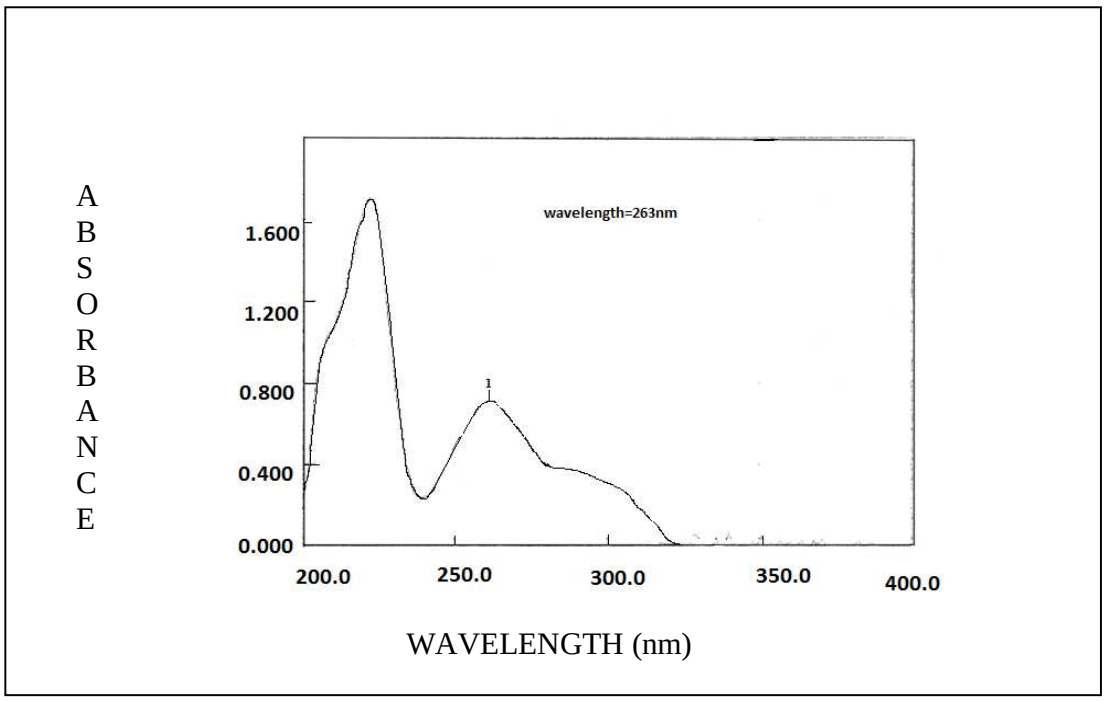


Fig. 18: Absorption maximum of Mebeverine in Phosphate buffer pH 6.8

Table 20: Concentration and Absorbance data for Calibration Curve of Mebeverine in Phosphate buffer pH 6.8

S. No.	Concentrations (µg/ml)	Absorbance at 263 nm
1	Blank	0
2	5	0.165
3	10	0.291
4	15	0.424
5	20	0.584
6	25	0.728

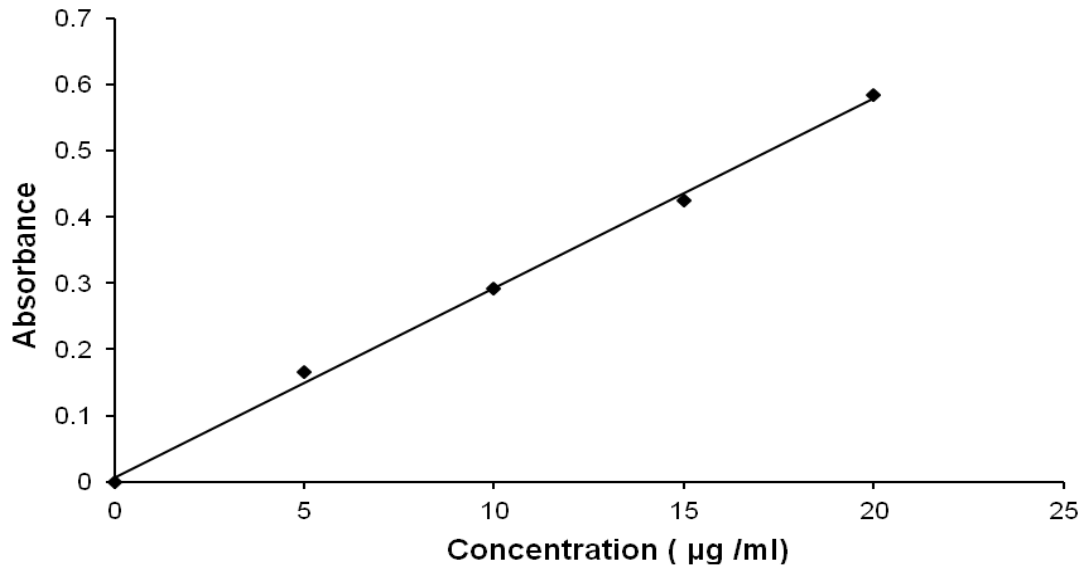


Fig. 19: Calibration Curve of Mebeverine in Phosphate buffer pH 6.8

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 21.

Table 21: Data for Calibration Curve parameters of Mebeverine in Phosphate buffer pH 6.8

S. No.	Parameters	Values
1	Slope	0.0285
2	Intercept	0.0074
3	Correlation coefficient (R)	0.9993

9.1.4.1.4. Determination of λmax and Preparation of Calibration Curve of Mebeverine by using Phosphate buffer pH 7.4:

UV absorption spectrum of Mebeverine in pH7.4 phosphate buffer shows λmax at 263 nm. Absorbance obtained for various concentrations of Mebeverine was found to be linear in the concentration range of 5 – 25 µg /ml. The Mebeverine absorbance in Phosphate buffer pH 7.4 is given in Table 22. The graph of absorbance concentration for drug obeys Beer- Lambert's law in the range of 5 – 25 µg /ml.

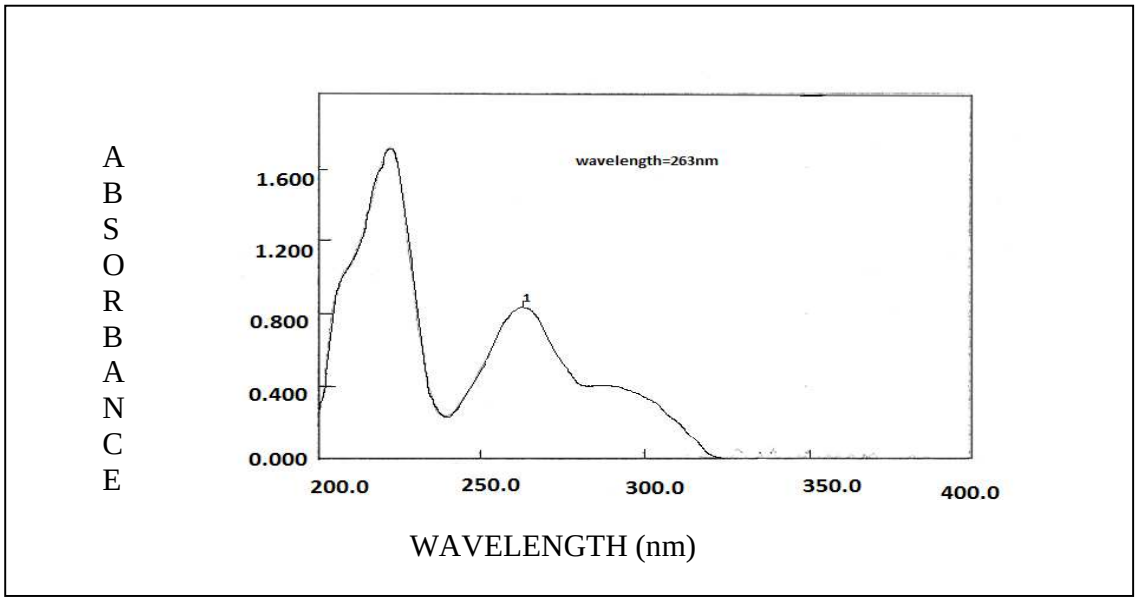


Fig. 20: Absorption maximum of Mebeverine in Phosphate buffer pH 7.4

Table 22: Concentration and Absorbance data for Calibration Curve of Mebeverine in Phosphate buffer pH 7.4

S. No.	Concentration (µg/ml)	Absorbance at 263 nm
1	blank	0
2	5	0.144
3	10	0.333
4	15	0.524
5	20	0.734
6	25	0.945

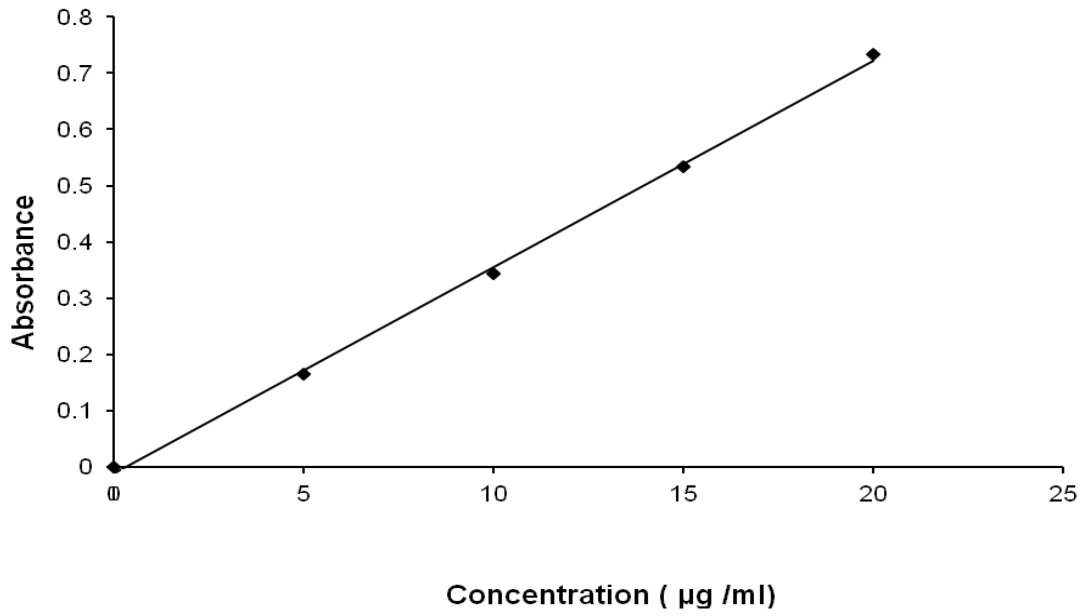


Fig. 21: Calibration curve of Mebeverine in Phosphate buffer pH 7.4

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the following table23.

Table 23: Data for Calibration Curve parameters of Mebeverine in Phosphate buffer pH 7.4

S. No.	Parameters	Values
1	Slope	0.037
2	Intercept	-0.0226
3	Correlation coefficient (R)	0.9996

9.1.4.2. Fourier Transform Infra-Red Spectroscopy (FTIR):

The IR spectrum of Mebeverine is shown in figure 22. The Interpretation of IR frequencies are shown in Table 24.

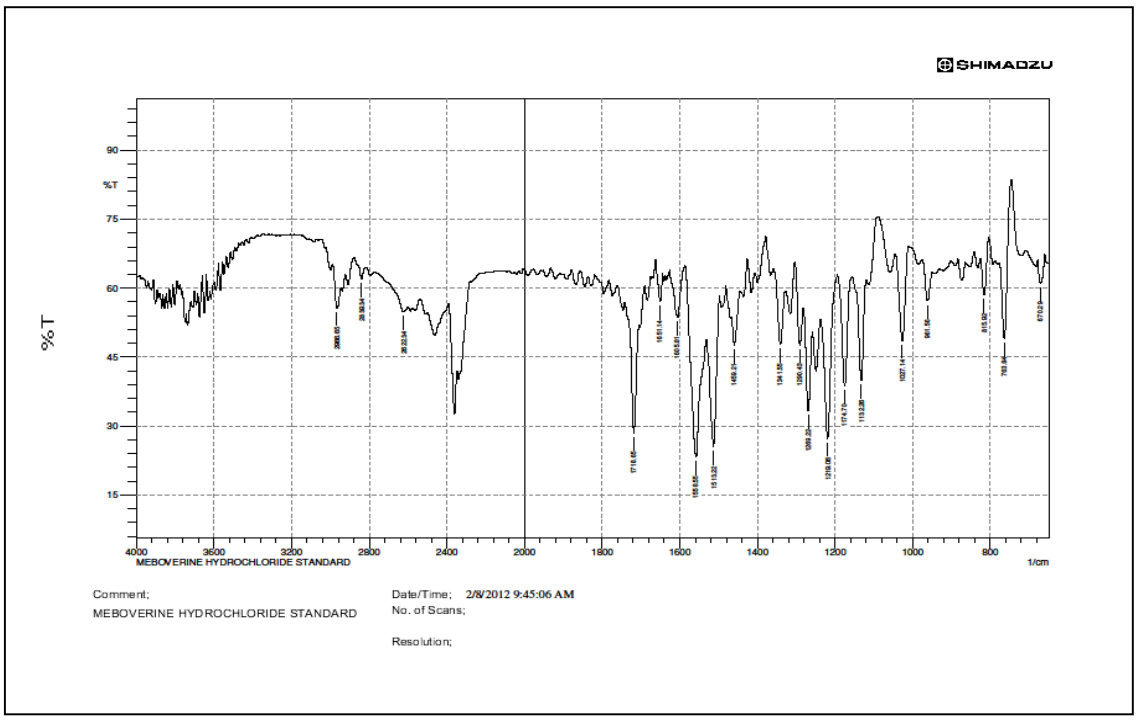


Fig. 22: IR Spectrum of Mebeverine HCl

Interpretation of IR Spectrum:

Table 24 shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Mebeverine. Hence, the sample was confirmed as Mebeverine HCl.

Table 24: Characteristic Frequencies in IR Spectrum of Mebeverine

Functional groups	Wave No. ($cm^{-1)}$
C-H Stretching	2995.58
C=O Stretching	1717.68
C=C Ring stretch	1559.51-1509.36
C-N Stretching	1399.62

9.1.5. Loss on drying:

The percentage loss on drying after 5 hours was found to be 0.208±0.003%. The sample passes test for loss on drying as per the limits specified in IP.

Table 25: Loss on drying of Mebeverine

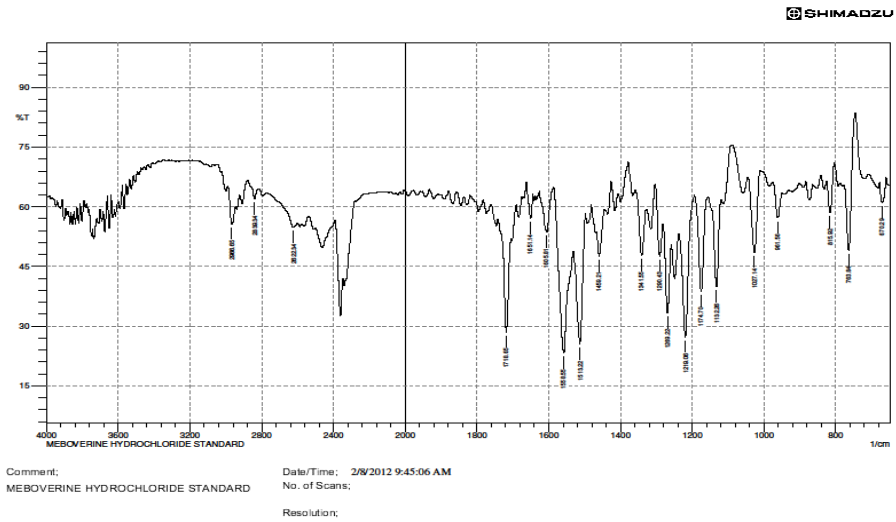
S. No.	Percentage Loss on drying (%)	Average LOD (%)
1	0.205	0.208±0.003
2	0.206	
3	0.214	

All the values are expressed as a mean ± SD., n = 3

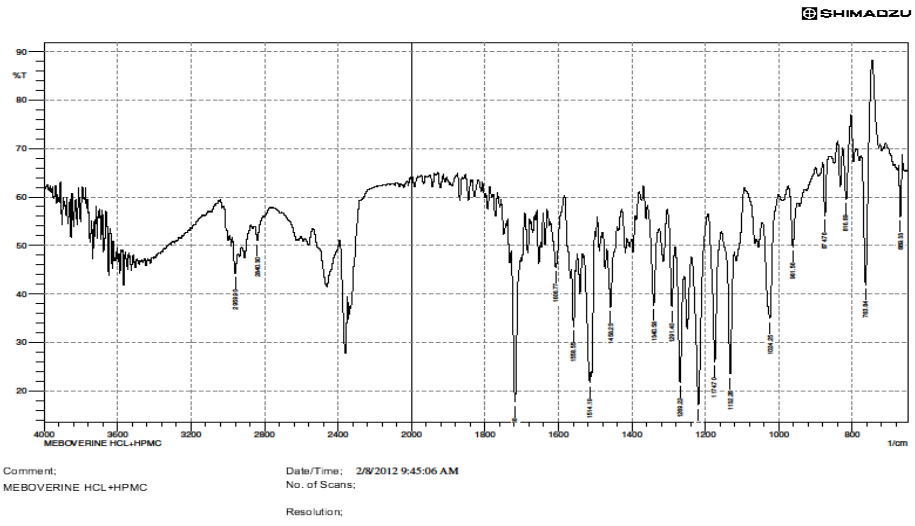
9.2. DRUG - POLYMERS COMPATIBILITY STUDIES:

9.2.1. Fourier Transform Infra-Red Spectroscopy (FTIR):

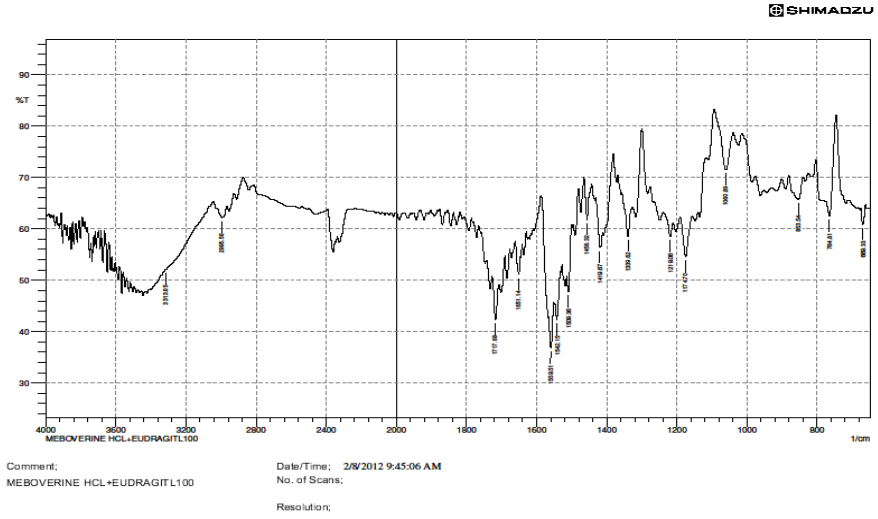
A.



B.



C.



D.

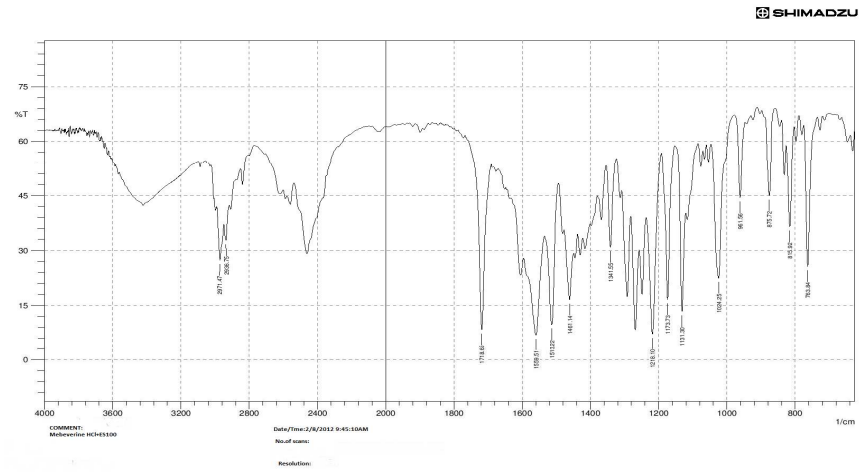


Fig. 23: IR Spectra of

A. Mebeverine HCl.

B. Mebeverine HCl + HPMC K4M

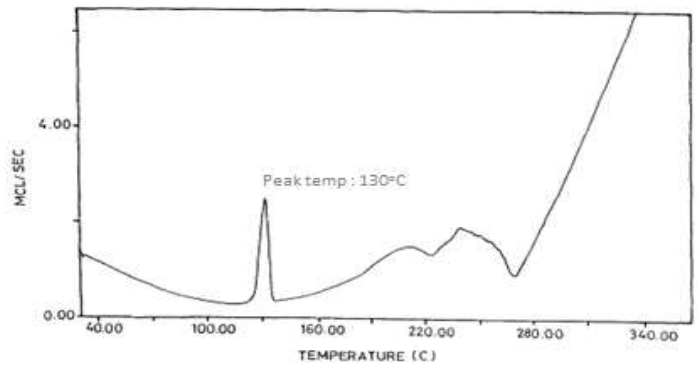
C. Mebeverine HCl + Eudragit L100

D. Mebeverine HCl + Eudragit S100

From the above figures, it can be seen that, the major functional group peaks observed in spectra's of Mebeverine with HPMC K4M, Mebeverine with Eudragit L100 and Mebeverine with Eudragit S100 remains unchanged as compared with spectra of Mebeverine HCl. So from the above IR spectra it can be observed that there is no interaction between Mebeverine HCl and Polymers used in the formulations.

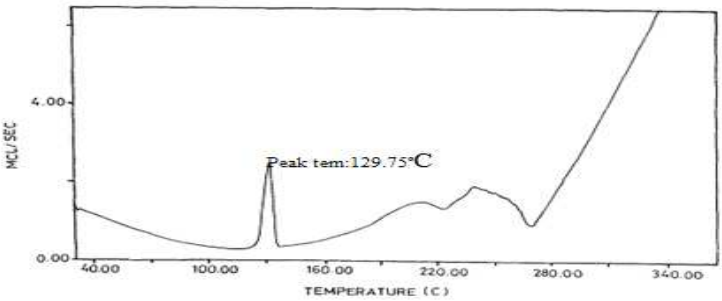
9.2.2. Differential Scanning Calorimetry (DSC):

A.



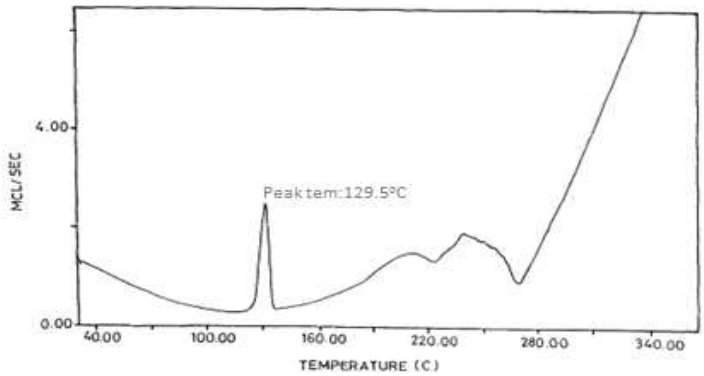
Thermal Curve of Mebeverine Hydrochloride

B.



Thermal curve of Mebeverine hydrochloride +E L100

C.



Thermal curve of Mebeverine hydrochloride+HPMC

D.

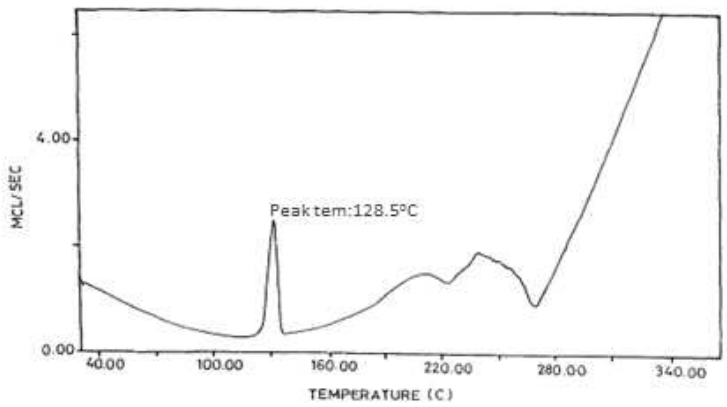


Fig.24. Thermo gram of **A. Mebeverine HCl**
B. Mebeverine HCl + Eudragit L100
C. Mebeverine HCl + HPMC
D. Mebeverine HCl+ Eudragit S100

The results of DSC studies are given in above figures. Pure Mebeverine HCl showed sharp endotherm at 130°C corresponding to its melting point. There was no appreciable change in the melting endotherms of Mebeverine with HPMC K4M, Mebeverine with Eudragit L100 and Mebeverine with Eudragit S100 as compared to the thermo gram of Mebeverine HCl. So, it could be concluded that there is no interaction between Mebeverine HCl and Polymers used in the formulations.

9.3. MICROMERITIC PROPERTIES OF MEBEVERINE HCl MICROPELLETS:

9.3.1. Appearance:

Table 26: General appearance study of micropellets

Parameters	Fc	F1-F3	F4-F6	F6-F9
Composition	----	Eudragit L100	Eudragit S100	Both Eudragit L100 and Eudragit S100
Shape	Spherical	Spherical	Spherical	Spherical
Size by visualization	Small	Large than control	Large in size	Large in size
Colour	Creamish white	More white than control	White pellets	White pellets
Stickiness	None	None	None	None
Odour	No	No	No	No

9.3.1.1. Appearance:

The scanning electron microscope shows the pellets being spheroid in shape and showing smooth surface of pellets.

9.3.2. Particle size:

Table 27: particle size for various formulations of micropellets

Formulations Code	Particle size (µm ± S.D)
F1	500±0.50
F2	640±0.32
F3	690±0.41
F4	610±0.45
F5	670±0.43
F6	658±0.32
F7	759±0.34
F8	789±0.54
F9	775±0.36

All the values are expressed as a mean ± SD., n = 3

9.3.2.1. Particle size:

The size of micro pellets found to be in the range of 500 µm to 790 µm and it was observed that increase in concentration of coating polymer particle size of the micro pellets significantly increased. The average particle size is highest for F8. The particle size distribution is uniform and narrow.

Table 28: Micromeritic Properties of Prepared micropellets

Formulations Code	Angle of Repose (^{o})	BD (gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	24.23±0.02	0.923±0.01	0.989±0.01	5.47	1.07
F2	24.23±0.02	0.931±0.01	0.984±0.01	5.71	1.05
F3	24.48±0.04	0.921±0.03	0.988±0.04	4.38	1.07
F4	25.06±1.06	0.934±0.01	0.991±0.02	4.96	1.06
F5	23.93±0.19	0.915±0.01	0.959±0.03	5.21	1.04
F6	25.18±0.33	0.952± 0.03	0.999±0.06	5.47	1.04
F7	25.92±0.15	0.947±0.01	1.028±0.01	5.39	1.08
F8	24.72±0.15	0.928±0.04	0.972±0.03	5.11	1.04
F9	23.31±0.04	0.938±0.06	0.987±0.05	4.96	1.05

All the values are expressed as a mean ± SD., n = 3

9.3.3. Angle of repose:

The results for angle of repose are recorded in Table 28. Angle of repose ranged from 23.31 ± 0.04 to 25.92 ± 0.15. The flow properties of micropellets in all formulations exhibit good flow.

9.3.4. Bulk density and Tapped bulk density:

The results are shown in Table 28. The values of BD and TBD were found to be in the range from 0.915±0.01 to 0.952±0.03 gm/ml and from 0.999±0.06 to 1.028±0.01 gm/ml respectively. So, it shows that all formulations having good flow properties and pack ability.

9.3.5. Carr's Compressibility Index:

The results for Carr's Compressibility Index are recorded in Table 28. The Carr's Compressibility Index were in the ranged from 4.38 to 5.71 %. This indicates good flow properties of micropellets.

9.3.6. Hausner's ratio:

The result were summarized in Table 28. The Hausner's ratio were found in the ranged from 1.04 to 1.08. So it indicates good flow properties.

9.4. EVALUATION OF MEBEVERINE HCl MICROPELLETS:

Table 29: Physico-Chemical Properties of micropellets:

Formulations Code	Drug Content* (%)	Loose surface crystal (%)	Loss on drying (%)
F1	99.05±0.02	3.201	0.9
F2	99.30±0.02	2.360	0.8
F3	98.6±0.015	1.990	0.8
F4	98.85±0.030	3.891	0.9
F5	99.2±0.028	3.237	0.7
F6	98.65±0.025	2.569	0.7
F7	99.05±0.036	1.786	0.9
F8	99.65±0.040	1.463	0.8
F9	99.75±0.026	1.589	0.8

All the values are expressed as a mean ± SD., n = 3

9.4.1. Drug Content:

Drug content was found to be uniform among different batches of micropellets and ranged from 98.6 to 99.75 %. These results showed that the all formulations having percentage drug content within the specified limits as per IP.

9.4.2. Loose surface crystal study:

Loose surface crystal study was an important parameter giving an indication of the amount of the drug on the surface of the micropellets without proper entrapment. It also conforms net drug loss during process is minimal. With the increase in the copolymer concentration % LSC decreased significantly owing to high entrapment of drug in the dense network of polymer.

9.4.3. Loss on drying:

The value of loss on drying was found from 0.7-0.9% and obese the pharmacopeia limits (Less than 1%).

9.4.4. Scanning electron microscope (SEM):

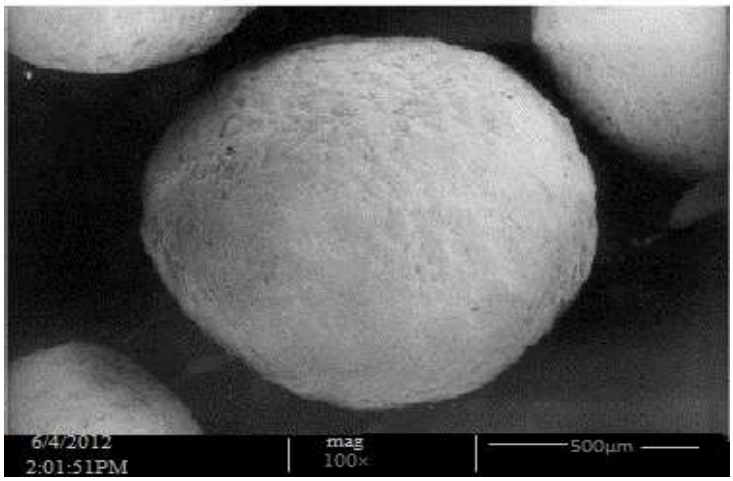


Fig.25: Scanning electron microscopy of mebeverine HCl loaded micropellets with Eudragit L100

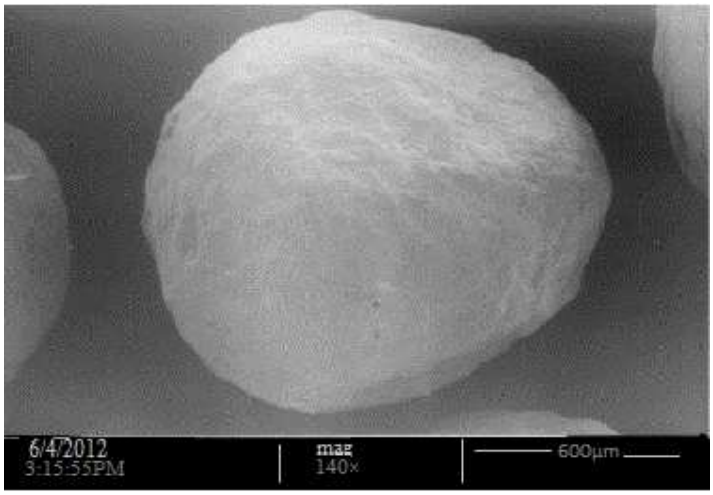


Fig.26: Scanning electrone microscopy of mebeverine HCl loaded micropellets with Eudragit S100

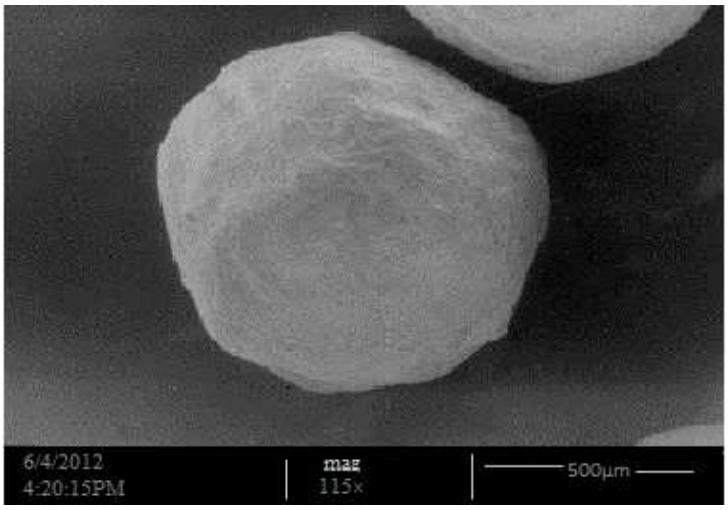


Fig.27: Scanning electrone microscopy of mebeverine HCl loaded micropellets with Eudragit S100 and Eudragit S100.

The scanning electron microscope shows the pellets being spheroid in shape. Surface depression was noted at the point of contact on the drying paper. On comparison of the pellets prepared from polymer s in high concentrations more roughness was observed with Eudragit polymers. Eudragit S100 produces more smooth surface area as compared to others.

9.5. *IN-VITRO* DRUG RELEASE STUDIES:

9.5.1. *IN-VITRO* DRUG RELEASE PROFILE OF MICROPELLETS:

- **Drug release Profile for Formulation F1:**

Table 30: *In-vitro* drug release data of Formulation F1

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	6.19±0.015	0.72	1.81	0.50	6.19
3		2	6.92±0.010	0.80	2.80	0.59	6.99
4	pH 6.8 phosphate buffer	3	10.95±0.010	1.20	3.54	1.24	11.02
5		4	17.44±0.025	1.85	4.56	2.03	17.51
6		5	21.04±0.030	2.22	5.69	2.44	21.11
7	pH 7.4 phosphate buffer	6	51.32±0.030	5.24	7.85	4.20	51.39
8		7	71.5±0.041	7.27	11.19	4.84	71.57
9		8	74.53±0.020	7.61	14.44	4.96	74.60
10		10	75.69±0.011	7.77	19.24	5.04	75.76
11		12	76.98±0.020	7.94	22.58	5.17	77.05

All the values are expressed as a mean ± SD., n = 3

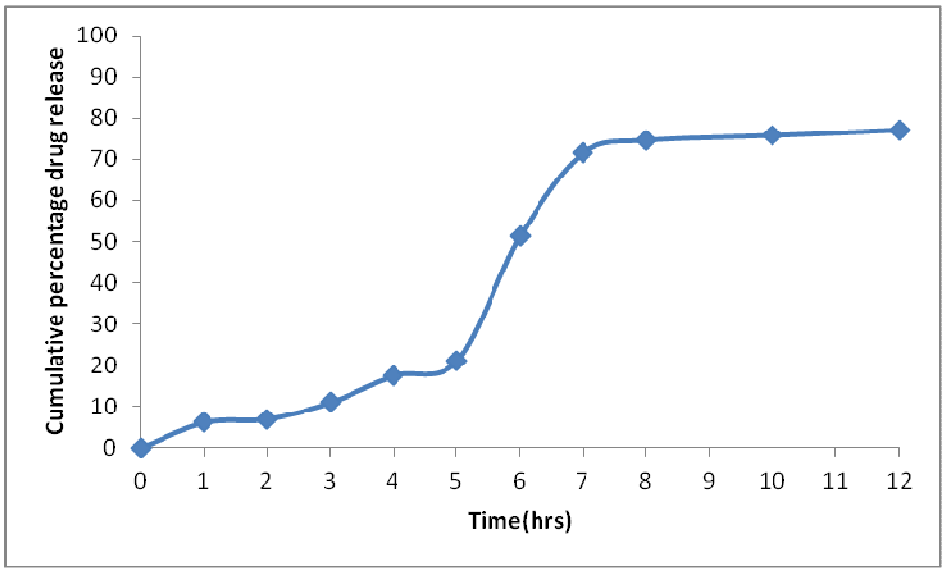


Fig.28. Cumulative percentage Drug release profile of F1.

❖ **Drug release Profile for Formulation F2:**

Table 31: *In-vitro* drug release data of Formulation F2

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.61±0.057	0.69	1.73	0.50	5.61
3		2	6.48±0.020	0.75	2.68	0.58	12.09
4	pH 6.8 phosphate buffer	3	10.09±0.025	1.13	3.36	1.22	15.70
5		4	17.01±0.015	1.81	4.35	2.07	22.62
6		5	20.47±0.020	2.16	5.47	2.47	26.08
7	pH 7.4 phosphate buffer	6	50.60±0.020	5.16	7.61	4.23	56.21
8		7	71.65±0.020	7.28	10.97	4.89	77.26
9		8	75.25±0.030	7.68	14.27	5.03	80.86
10		10	76.55±0.025	7.85	19.18	5.11	82.16
11		12	77.85±0.026	8.02	22.60	5.24	83.46

All the values are expressed as a mean ± SD., n = 3

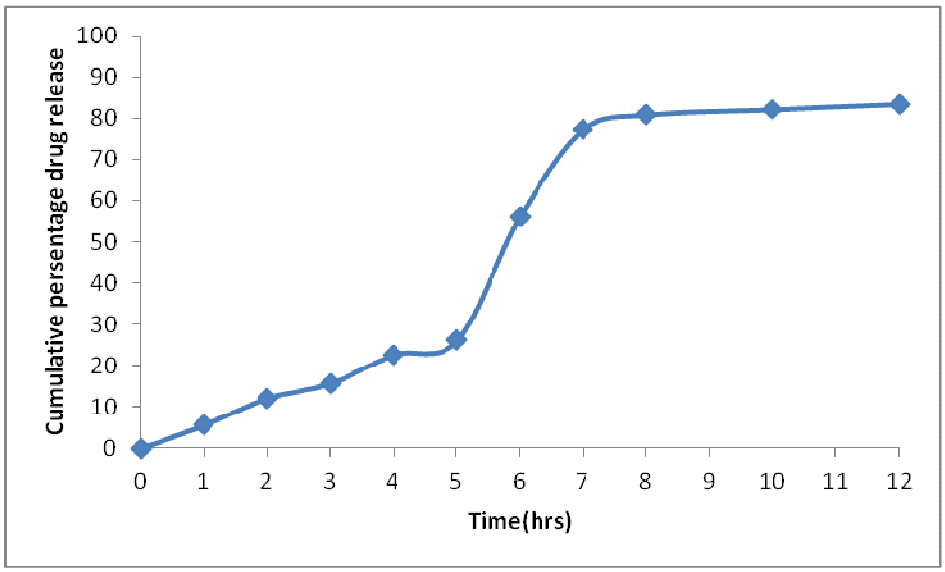


Fig.29. Cumulative percentage Drug release profile of F2

❖ **Drug release Profile for Formulation F3:**

Table 32: *In-vitro* drug release data of Formulation F3

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.19±0.01	0.62	1.56	0.50	5.91
3		2	6.05±0.020	0.71	2.44	0.63	11.24
4	pH 6.8 phosphate buffer	3	9.51±0.015	1.06	3.10	1.24	14.70
5		4	16.00±0.025	1.71	4.06	2.10	21.19
6		5	19.75±0.020	2.09	5.14	2.54	24.94
7	pH 7.4 phosphate buffer	6	46.42±0.025	4.75	7.14	4.20	51.61
8		7	69.05±0.025	7.02	10.32	4.94	74.24
9		8	73.09±0.036	7.46	13.55	5.09	78.28
10		10	74.10±0.020	7.60	18.37	5.17	79.29
11		12	75.11±0.030	7.74	21.70	5.27	80.30

All the values are expressed as a mean ± SD., n = 3

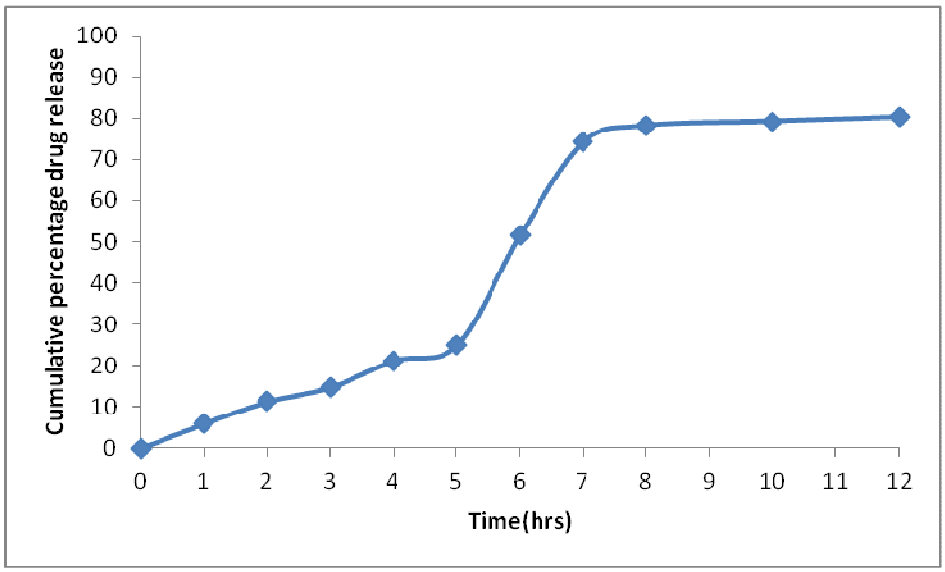


Fig.30. Cumulative percentage Drug release profile of F3

❖ **Drug release Profile for Formulation F4:**

Table 33: *In-vitro* drug release data of Formulation F4

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	6.77±0.036	0.82	2.06	0.50	6.77
3		2	8.07±0.011	0.97	3.26	0.65	14.84
4	pH 6.8 phosphate buffer	3	11.67±0.015	1.36	4.12	1.19	18.44
5		4	18.45±0.02	2.11	5.26	2.00	25.22
6		5	22.34±0.030	2.54	6.53	2.43	29.11
7	pH 7.4 phosphate buffer	6	54.35±0.026	6.02	9.01	4.21	61.12
8		7	74.10±0.045	8.20	12.80	4.81	80.87
9		8	77.27±0.040	8.59	16.45	4.94	84.04
10		10	79.43±0.020	8.87	21.89	5.06	86.20
11		12	81.60±0.026	9.15	25.75	5.25	88.37

All the values are expressed as a mean ± SD., n = 3

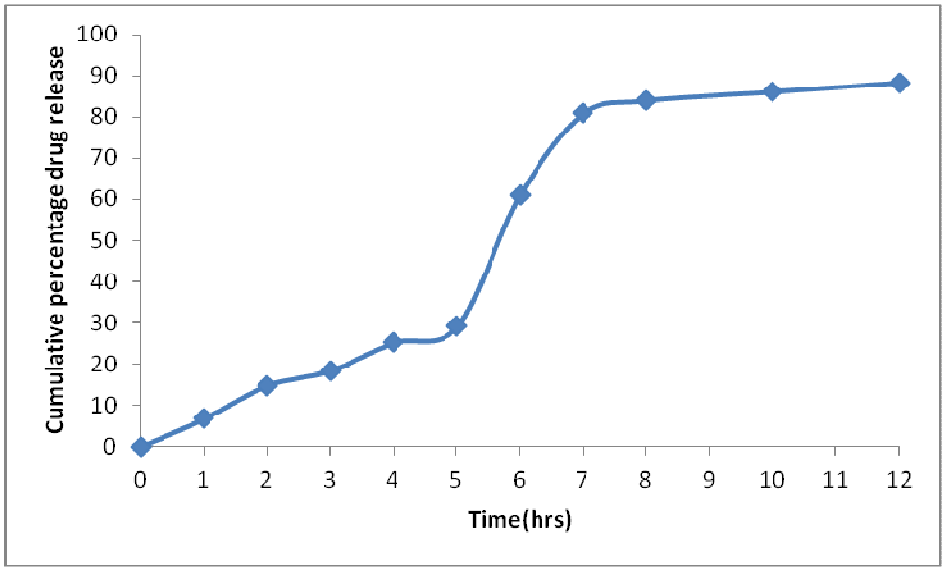


Fig.31. Cumulative percentage Drug release profile of F4

❖ **Drug release Profile for Formulation F5:**

Table 34: *In-vitro* drug release data of Formulation F5

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	6.34±0.026	0.78	1.94	0.50	6.34
3		2	7.06±0.032	0.86	3.01	0.60	13.40
4	pH 6.8 phosphate buffer	3	10.95±0.015	1.28	3.79	1.23	17.29
5		4	17.58±0.020	2.01	4.90	2.05	23.92
6		5	21.48±0.010	2.44	6.15	2.48	27.82
7	pH 7.4 phosphate buffer	6	52.04±0.015	5.77	8.55	4.22	58.38
8		7	72.23±0.025	7.99	12.24	4.86	78.57
9		8	76.55±0.030	8.51	15.87	5.01	82.89
10		10	79.00±0.020	8.82	21.36	5.16	85.34
11		12	81.31±0.015	9.12	25.27	5.35	87.65

All the values are expressed as a mean ± SD., n = 3

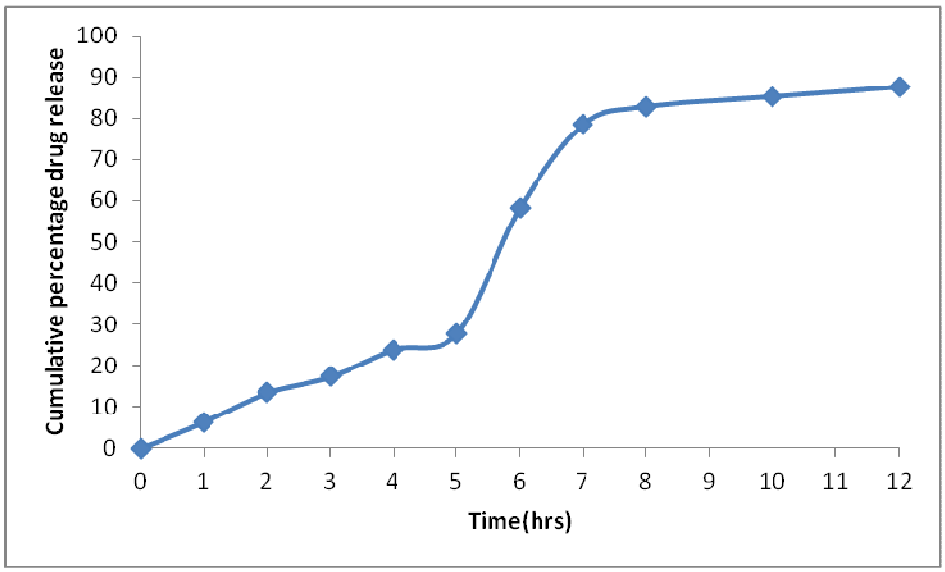


Fig.32. Cumulative percentage Drug release profile of F5

❖ **Drug release Profile for Formulation F6:**

Table 35: *In-vitro* drug release data of Formulation F6

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.91±0.030	0.73	1.82	0.50	5.91
3		2	6.63±0.045	0.81	2.83	0.60	12.45
4	pH 6.8 phosphate buffer	3	10.09±0.015	1.19	3.56	1.21	15.91
5		4	16.72±0.020	1.92	4.61	2.08	22.54
6		5	21.04±0.02	2.40	5.84	2.56	26.86
7	pH 7.4 phosphate buffer	6	49.88±0.028	5.54	8.17	4.23	55.70
8		7	70.35±0.030	7.79	11.76	4.88	76.17
9		8	72.66±0.025	8.08	15.25	4.98	78.48
10		10	76.41±0.032	8.53	20.51	5.19	82.23
11		12	79.29±0.020	8.89	24.35	5.43	85.11

All the values are expressed as a mean ± SD., n = 3

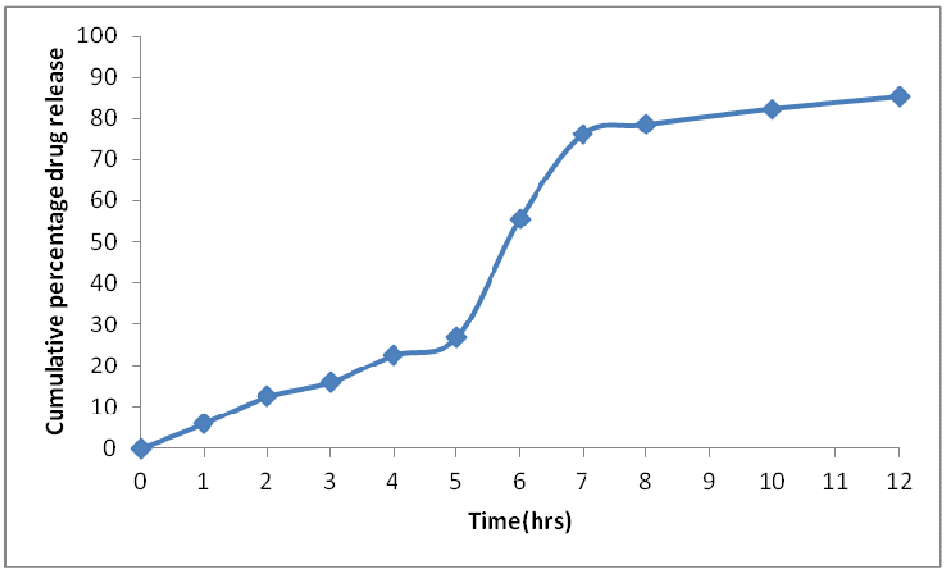


Fig.33. Cumulative percentage Drug release profile of F6

❖ **Drug release Profile for Formulation F7:**

Table 36: *In-vitro* drug release data of FormulationF7

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.62±0.025	0.84	2.10	0.50	5.62
3		2	6.34±0.015	0.90	3.23	0.57	11.96
4	pH 6.8 phosphate buffer	3	9.80±0.010	1.19	3.90	1.03	15.42
5		4	16.14±0.020	1.71	4.74	1.79	21.76
6		5	20.04±0.015	2.04	5.67	2.22	25.66
7	pH 7.4 phosphate buffer	6	54.20±0.025	4.83	7.59	4.12	59.82
8		7	73.38±0.025	6.42	10.52	4.71	79.00
9		8	77.99±0.021	6.83	13.35	4.87	83.61
10		10	82.03±0.020	7.20	17.69	5.08	87.65
11		12	83.75±0.015	7.29	20.78	5.16	89.37

All the values are expressed as a mean ± SD., n = 3

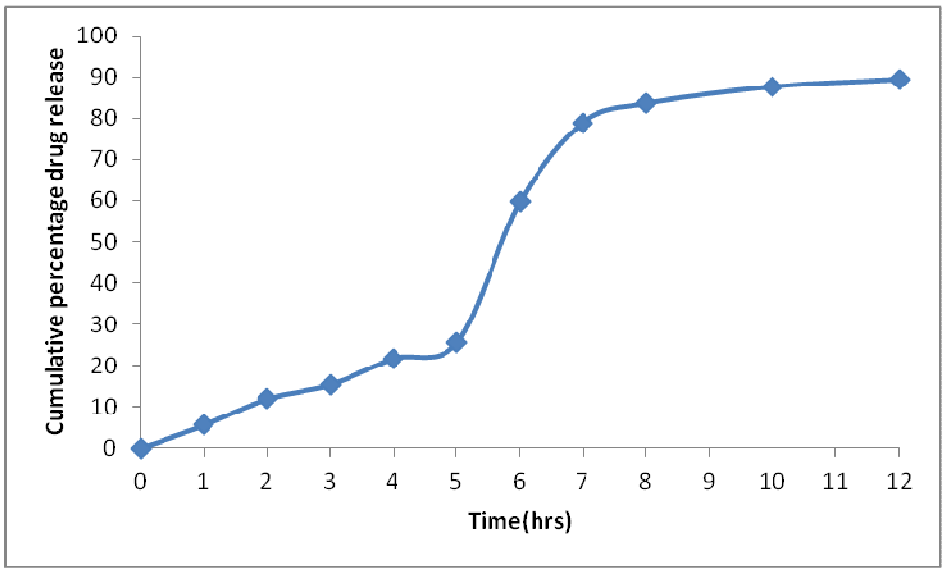


Fig.34. Cumulative percentage Drug release profile of F7

❖ **Drug release Profile for Formulation F8:**

Table 37: *In-vitro* drug release data of Formulation F8

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.76±0.020	0.85	2.13	0.50	5.76
3		2	6.77±0.02	0.94	3.30	0.59	12.53
4	pH 6.8 phosphate buffer	3	12.11±0.015	1.38	4.13	1.20	17.87
5		4	19.60±0.025	2.00	5.21	1.91	25.36
6		5	24.22±0.011	2.38	6.36	2.33	29.98
7	pH 7.4 phosphate buffer	6	56.08±0.03	4.99	8.37	3.99	61.83
8		7	74.68±0.025	6.53	11.29	4.58	80.438
9		8	76.84±0.020	6.74	14.03	4.67	82.59
10		10	80.44±0.015	7.07	18.13	4.87	86.99
11		12	80.88±0.02	7.15	21.03	4.94	87.43

All the values are expressed as a mean ± SD., n = 3

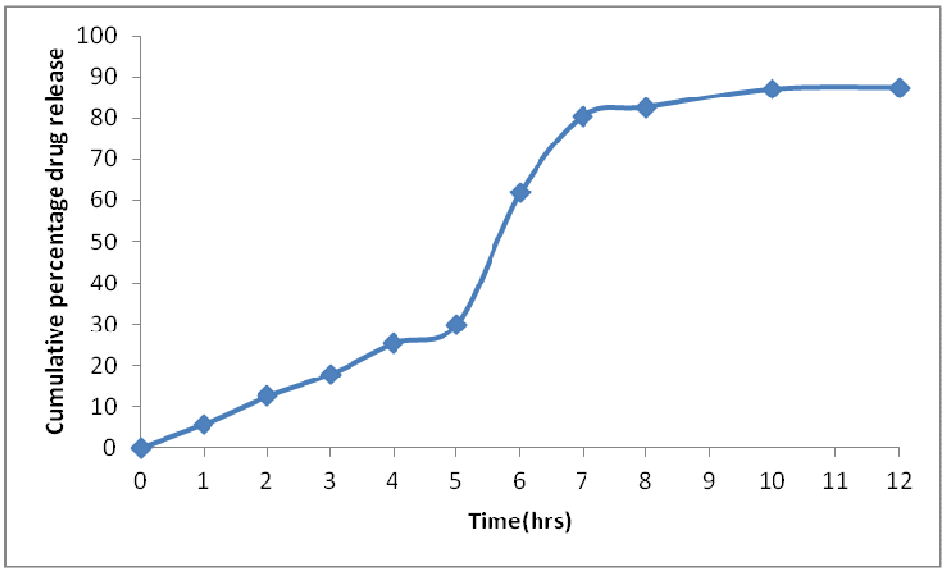


Fig.35. Cumulative percentage Drug release profile of F8

❖ **Drug release Profile for Formulation F9:**

Table 38: *In-vitro* drug release data of Formulation F9

S. No.	Medium	Time (hours)	Drug Release (%)	Amount of drug released (mg)	DE (%)	MDT (hrs)	Cumulative drug Release (%)
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	6.05±0.030	0.88	2.19	0.50	6.05
3		2	7.06±0.01	0.96	3.39	0.59	13.11
4	pH 6.8 phosphate buffer	3	11.67±0.025	1.34	4.18	1.13	17.74
5		4	19.17±0.025	1.96	5.20	1.88	25.24
6		5	23.78±0.036	2.35	6.32	2.31	29.85
7	pH 7.4 phosphate buffer	6	55.50±0.030	4.94	8.30	3.98	61.57
8		7	74.24±0.020	6.50	11.20	4.59	80.31
9		8	77.56±0.015	6.80	13.96	4.72	83.63
10		10	80.88±0.025	7.11	18.12	4.90	86.95
11		12	82.18±0.020	7.25	21.08	5.02	88.25

All the values are expressed as a mean ± SD., n = 3

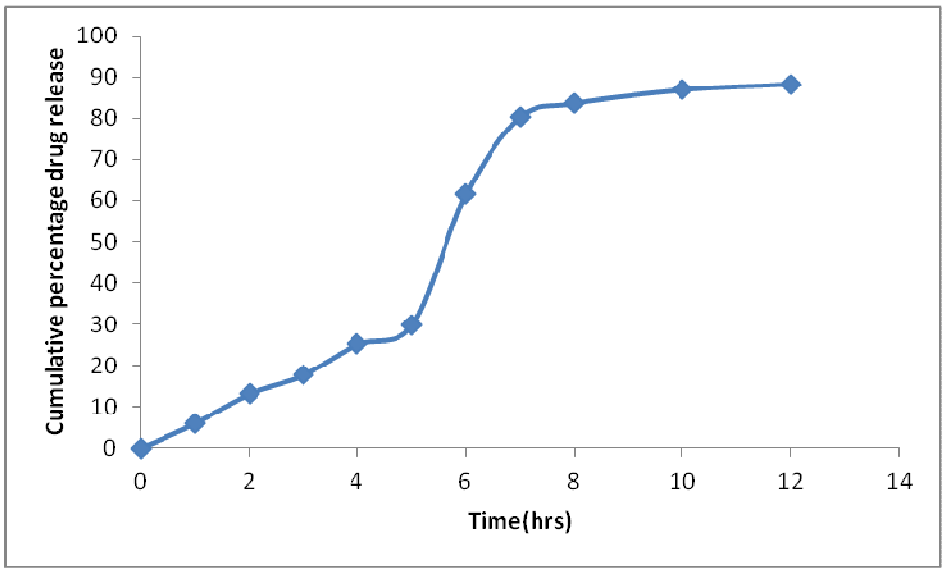


Fig.36. Cumulative % Drug release profile of formulation F9

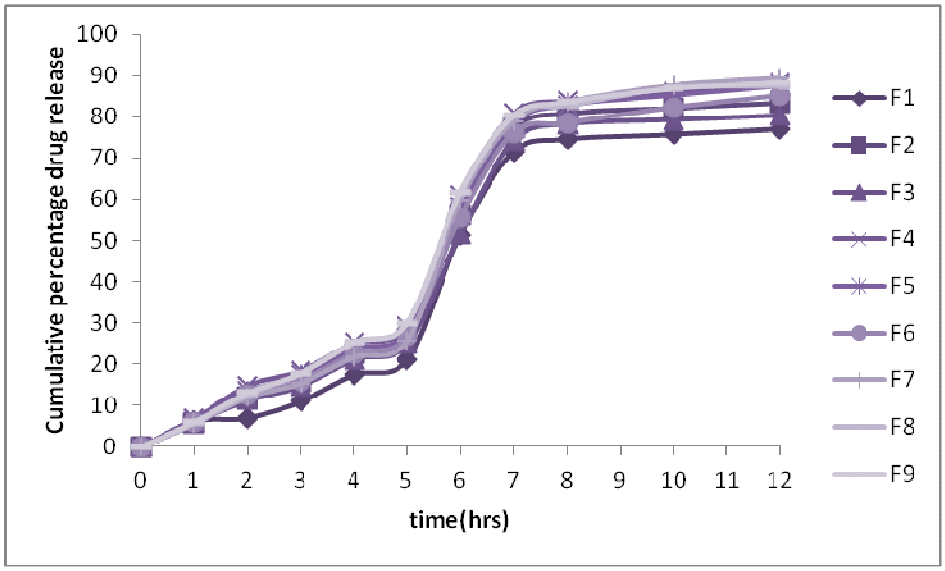


Fig.37. Cumulative % Drug release profile of formulation F1 – F9

The purpose of colon targeted drug delivery system is not only to protect the drug from being released in the physiological environment of the Stomach and Intestine but also to release the drug in the colon from the micropellets formulation. Hence the ability of the polymers used in the formulations (F1 to F9) to retain the integrity of pellets in upper GIT were assessed by conducting drug release studies in 0.1N HCl for 2 hours and pH 6.8 phosphate buffer for 3 hours (condition mimicking mouth to the colon transit). After 5 hours of testing not more than 30% of Mebeverine HCl was released from any formulations (F1 to F9). This shows that HPMC K4M, Eudragit L100, Eudragit S100 are capable of protecting the drug from being released completely in the physiological environment of Stomach and Small Intestine.

After completing the dissolution study in 0.1 N HCl (900ml) for first two hours and in phosphate buffer pH 6.8 (900ml) for next three hours, the dissolution study was continued in the phosphate buffer pH 7.4 up to the twelve hours.

The drug release from formulation F1, F2 and F3 containing Eudragit L100 (2%, 4% and 8%) alone was found to be 76.98%, 77.85% and 75.11% after the end of 12 hrs. This is due to lesser soluble of drug in the medium.

The drug released from formulation F4, F5 and F6 containing Eudragit S100 (2%, 4% and 8%) were 81.60%, 81.31% and 79.29% respectively at the end of 12 hrs.

The drug released from formulation F7, F8 and F9 containing Eudragit L100 and EudragitS100 were 83.75%, 80.88% and 82.18% respectively at the end of 12 hrs.

The drug released from formulation F7containing Eudragit L100 and Eudragit S100 was found to be 83.75% at the end of 12 hrs, which is showing high percentage drug release. It protects the drug at stomach pH and small intestine pH environment.

9.7. RELEASE DRUG DATA MODELING:

9.7.1. Kinetics of *in-vitro* drug release:

The drug diffusion through most type of polymeric system is often best described by Fickian diffusion (diffusion exponent, n=0.5), but other process in addition to diffusion are important. There is also a relaxation of the polymer chain, which influences the drug release mechanism. This process is described as non- fickian or anomalous diffusion (n=0.5-1.0). Release from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chain. The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is a special case of non- Fickian diffusion. To obtain kinetic parameter of dissolution profile, data were fitted to different kinetic models.

Table 39: Different Kinetic models for Formulations F1-F9

Code	Zero order		First order		Higuchi		Korsemayer's-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mg\ h^{-1/2}$)	R^2	n	
F1	0.9367	0.7878	0.9358	0.0082	0.8481	2.1188	0.9387	1.1424	Peppas
F2	0.9362	0.7907	0.9352	0.0082	0.8435	2.1220	0.9375	1.1688	Peppas
F3	0.9363	0.7610	0.9352	0.0079	0.8410	2.0394	0.9413	1.1892	Peppas
F4	0.9395	0.8917	0.9386	0.0093	0.8484	2.3955	0.9411	1.1533	Peppas
F5	0.9407	0.8782	0.9398	0.0092	0.8444	2.3530	0.9408	1.1848	Peppas
F6	0.9423	0.8490	0.9414	0.0088	0.8441	2.2727	0.9416	1.1975	Zero order
F7	0.9456	0.7139	0.9455	0.0074	0.8724	1.9362	0.9221	0.9358	zero order
F8	0.9466	0.7171	0.9468	0.0074	0.8883	1.9568	0.9387	0.9131	First order
F9	0.9985	0.7197	0.9487	0.0074	0.8869	1.9613	0.9356	0.9099	First order

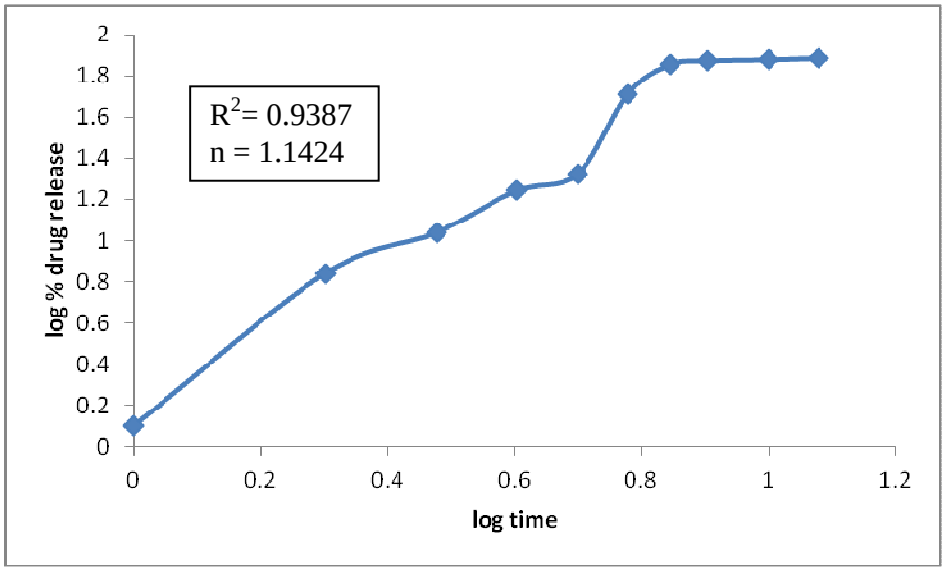


Fig. 38: Peppas plot of formulation F1

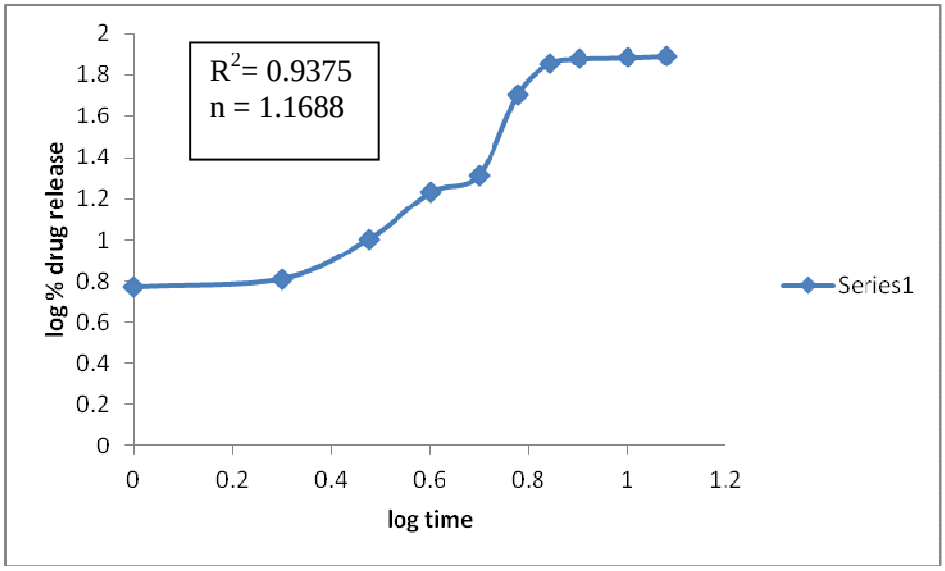


Fig. 39: Peppas plot of formulation F2

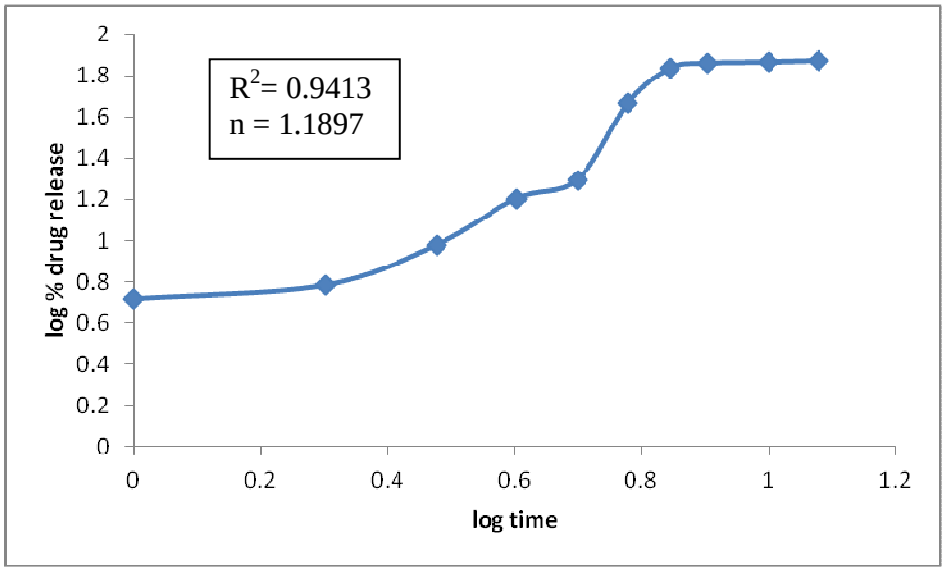


Fig. 40: Peppas plot of formulation F3

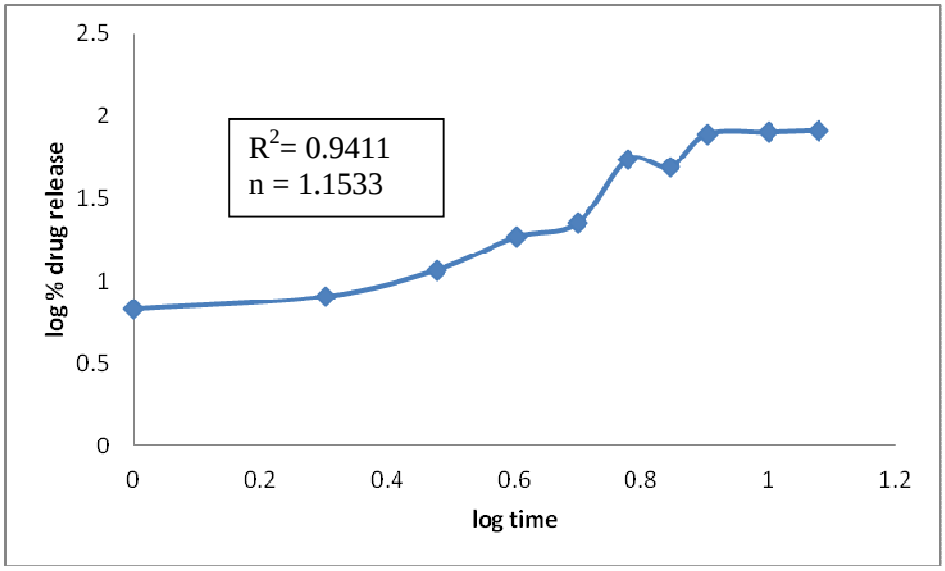


Fig. 41: Peppas plot of formulation F4

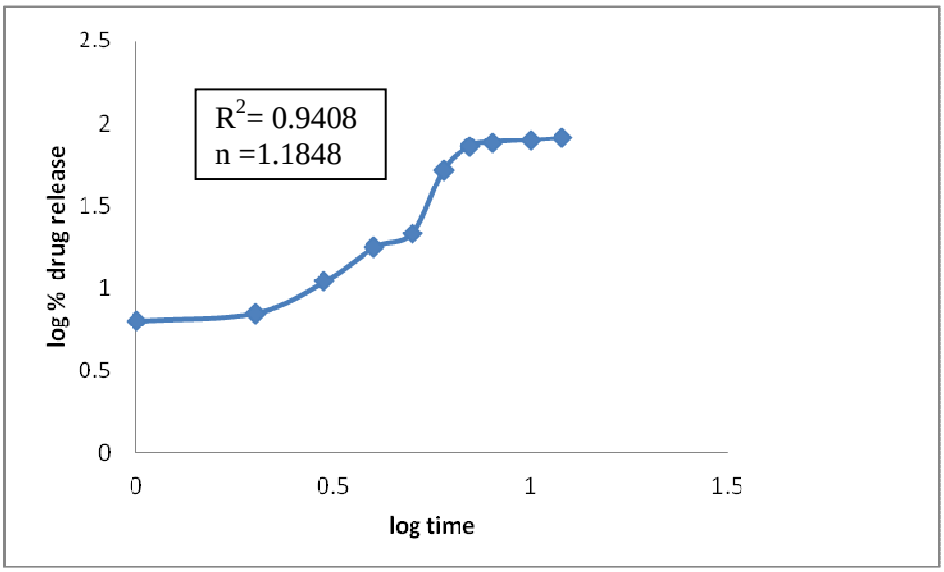


Fig. 42: Peppas plot of formulation F5

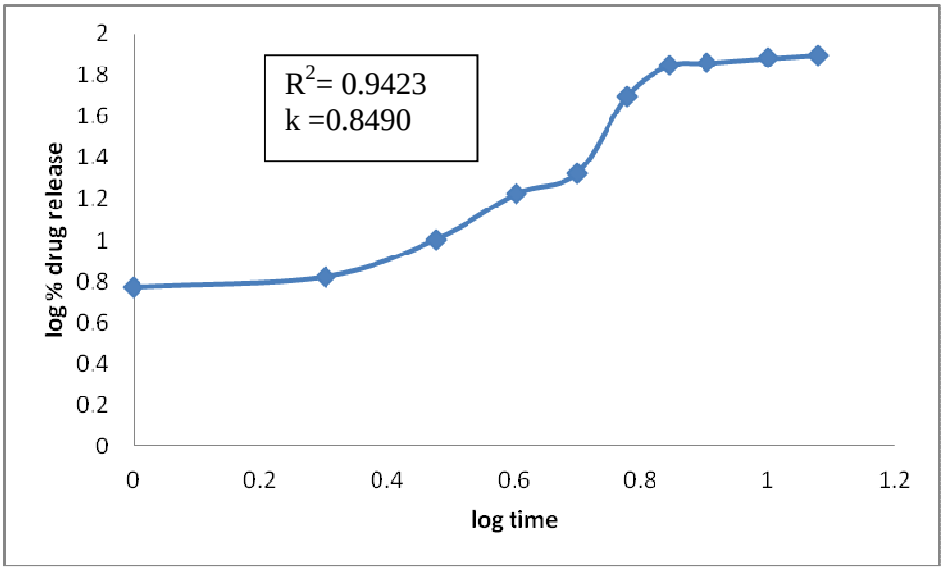


Fig. 43: Zero order plot of formulation F6

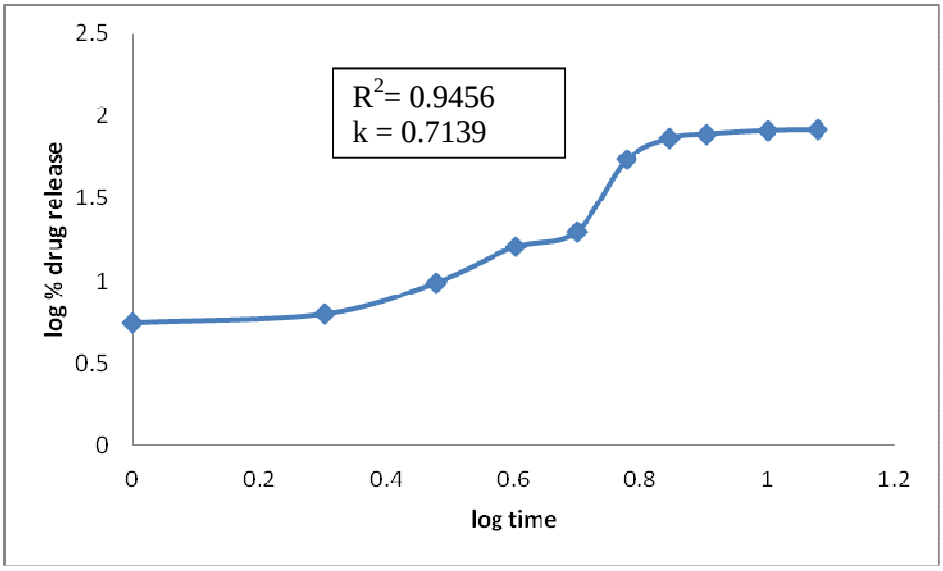


Fig. 44: Zero order plot of formulation F7

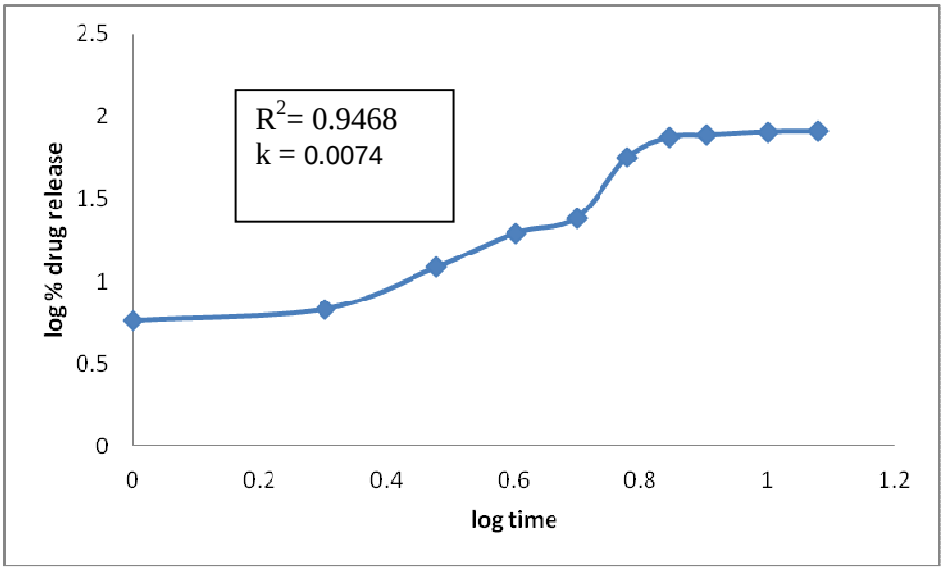


Fig. 45: First order plot of formulation F8

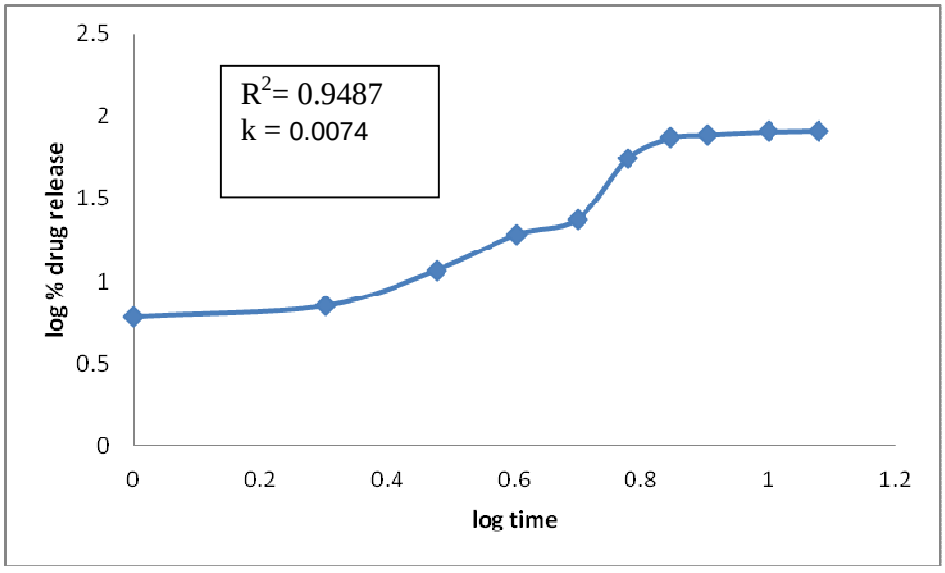


Fig. 46: First order plot of formulation F9

For micropellets, an “n” value near to 0.5 indicates diffusion control and an “n” value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism. It was also observed that highest correlation was found for Peppas log time profile (R^2 > 0.99), which indicates the drug release via diffusion mechanism from all formulations.

Drug release from the formulation F7 follows the zero order release mechanism because its R^2 value nearer to one.

9.8. STABILITY STUDIES

From the results of the above studies it was found that formulation F7 was considered as the best formulation amongst the nine formulations. Hence formulation F7 was selected for stability studies.

9.8.1. Stability studies at the end of First month (30 days):

9.8.1.1. Content Uniformity:

The Percentage drug content of pellets after one month of stability studies was studied. The results are within the official limits. The data is shown in Table 40.

Table 40: Drug content of formulation F7 at the end of 1 month of stability

S. No.	Formulation	Percentage drug content
1.	F7	98.50±0.030

All the values are expressed as a mean ± SD., n = 3

9.8.1.2. *In-vitro* drug release study:

The Cumulative Percentage Drug Release from F7 micropellets after one month of stability was studied. The data is shown in Table 41.

Table 41: *In-vitro* drug release data of formulation F7 at the end of 1 month of stability

S. No.	Medium	Time (hours)	% Drug Release	Amount of drug released (mg)	%DE	MDT (hrs)	Cumulative % drug Release
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.60±0.025	0.84	2.10	0.50	5.60
3		2	6.32±0.015	0.90	3.23	0.57	11.92
4	pH 6.8 phosphate buffer	3	9.78±0.010	1.19	3.90	1.03	15.38
5		4	16.13±0.020	1.71	4.74	1.79	21.73
6		5	20.00±0.015	2.04	5.67	2.22	25.6
7	pH 7.4 phosphate buffer	6	54.17±0.025	4.83	7.59	4.12	59.77
8		7	73.35±0.025	6.42	10.52	4.71	78.95
9		8	77.98±0.021	6.83	13.35	4.87	83.58
10		10	81.99±0.020	7.20	17.69	5.08	87.59
11		12	83.73±0.015	7.29	20.78	5.16	89.30

All the values are expressed as a mean ± SD., n = 3

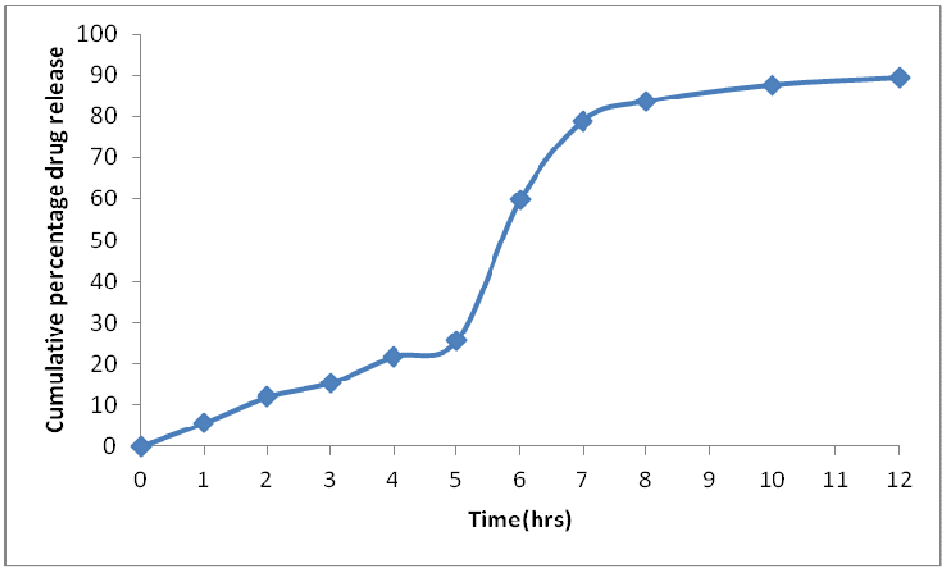


Fig.47. *In-vitro* drug release profile of formulation F7 at the end of 1 month of stability

9.8.2. Stability studies at the end of Second month (60 days):

9.8.2.1. Drug content:

The Percentage drug content of pellets after Two months of stability studies was studied. The results are within the official limits. The data is shown in Table 42.

Table 42: Drug content of formulation F7 at the end of 2 months of stability

Sl. No.	Formulation	Percentage drug content
1.	F7	98.15±0.025

All the values are expressed as a mean ± SD., n = 3

9.8.2.2. *In-vitro* drug release study:

The Cumulative Percentage Drug Release from F7 pellets after Two months of stability was studied. The data is shown in Table 43.

Table 43: *In-vitro* drug release data of formulation F7 at the end of 2 months of stability

Sl. No.	Medium	Time (hours)	% Drug Release	Amount of drug released (mg)	%DE	MDT (hrs)	Cumulative % drug Release
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.59±0.025	0.84	2.10	0.50	5.59
3		2	6.31±0.015	0.90	3.23	0.57	11.9
4	pH 6.8 phosphate buffer	3	9.77±0.010	1.19	3.90	1.03	15.36
5		4	16.10±0.020	1.71	4.74	1.79	21.69
6		5	19.99±0.015	2.04	5.67	2.22	25.58
7	pH 7.4 phosphate buffer	6	54.15±0.025	4.83	7.59	4.12	59.74
8		7	73.33±0.025	6.42	10.52	4.71	78.92
9		8	77.96±0.021	6.83	13.35	4.87	83.55
10		10	81.97±0.020	7.20	17.69	5.08	87.56
11		12	83.71±0.015	7.29	20.78	5.16	89.15

All the values are expressed as a mean ± SD., n = 3

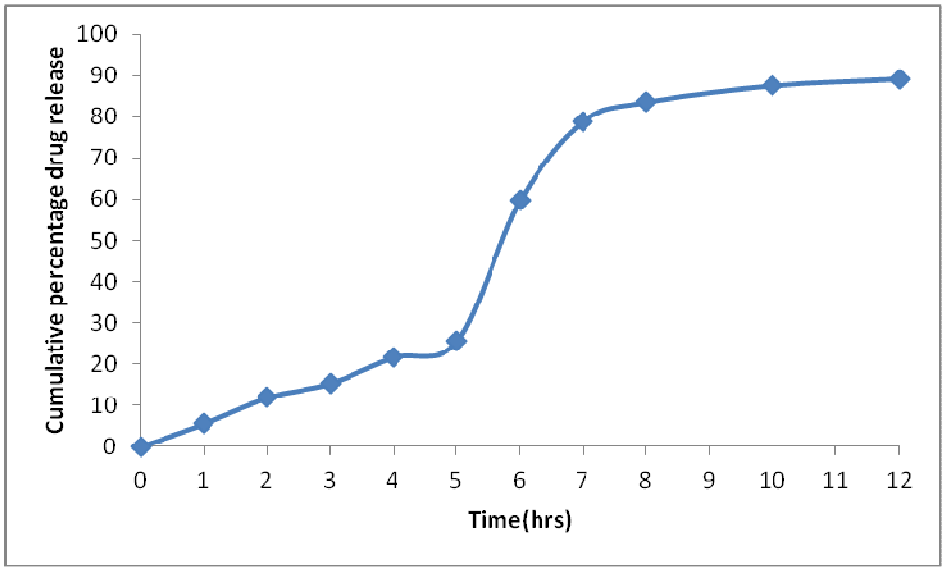


Fig.48. *In-vitro* drug release profile of formulation F7 at the end of 2 months of stability

9.8.3. Stability studies at the end of Third month (90 days):

9.8.3.1 Drug content:

The Percentage drug content of pellets after Third month of stability studies was studied. The results are within the official limits. The data is shown in Table 44.

Table 44: Drug content of formulation F7 at the end of 3 months of stability

Sl. No.	Formulation	Percentage drug content
1.	F7	97.75±0.020

All the values are expressed as a mean ± SD., n = 3

9.8.3.2. *In-vitro* drug release study:

The Cumulative Percentage Drug Release from F7 pellets after Two months of stability was studied. The data is shown in Table 45.

Table 45: *In-vitro* drug release data of formulation F7 at the end of 3 months of stability

Sl. No.	Medium	Time (hours)	% Drug Release	Amount of drug released (mg)	%DE	MDT (hrs)	Cumulative % drug Release
1		0	0	0.00	0.00	0.00	0
2	0.1N HCl	1	5.57±0.025	0.84	2.10	0.50	5.57
3		2	6.29±0.015	0.90	3.23	0.57	11.86
4	pH 6.8 phosphate buffer	3	9.76±0.010	1.19	3.90	1.03	15.33
5		4	16.08±0.020	1.71	4.74	1.79	21.65
6		5	19.97±0.015	2.04	5.67	2.22	25.54
7	pH 7.4 phosphate buffer	6	54.14±0.025	4.83	7.59	4.12	59.71
8		7	73.30±0.025	6.42	10.52	4.71	78.87
9		8	77.90±0.021	6.83	13.35	4.87	83.47
10		10	81.87±0.020	7.20	17.69	5.08	87.44
11		12	82.50±0.015	7.29	20.78	5.16	88.92

All the values are expressed as a mean ± SD., n = 3

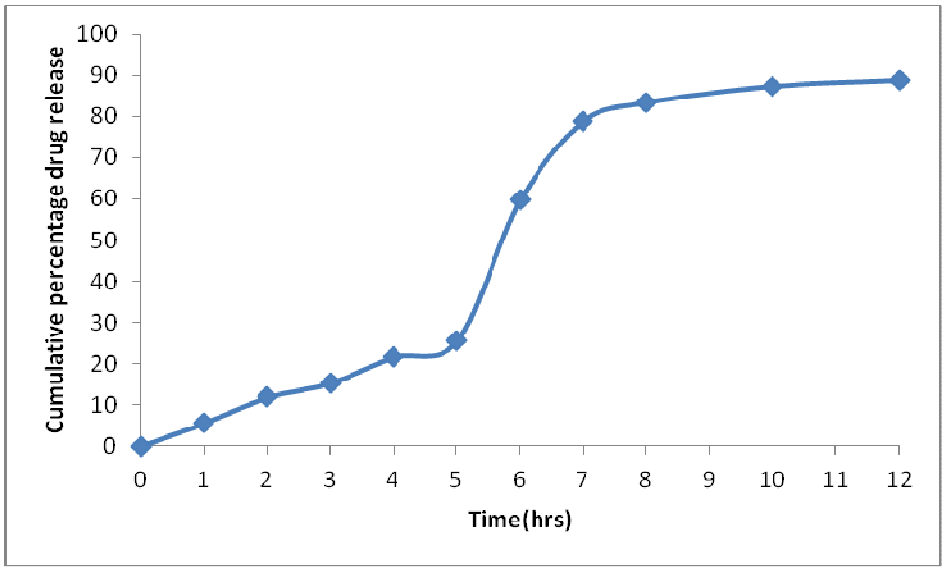


Fig.49. In-vitro drug release profile of formulation F7 at the end of 3months of stability

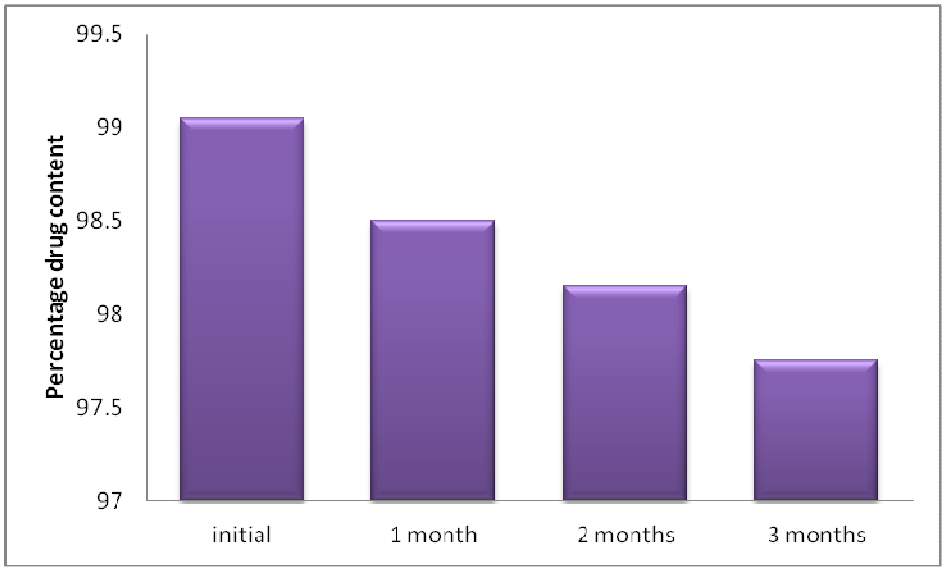


Fig.50. Comparison of drug content for formulation F7 with initial and different periods of stability

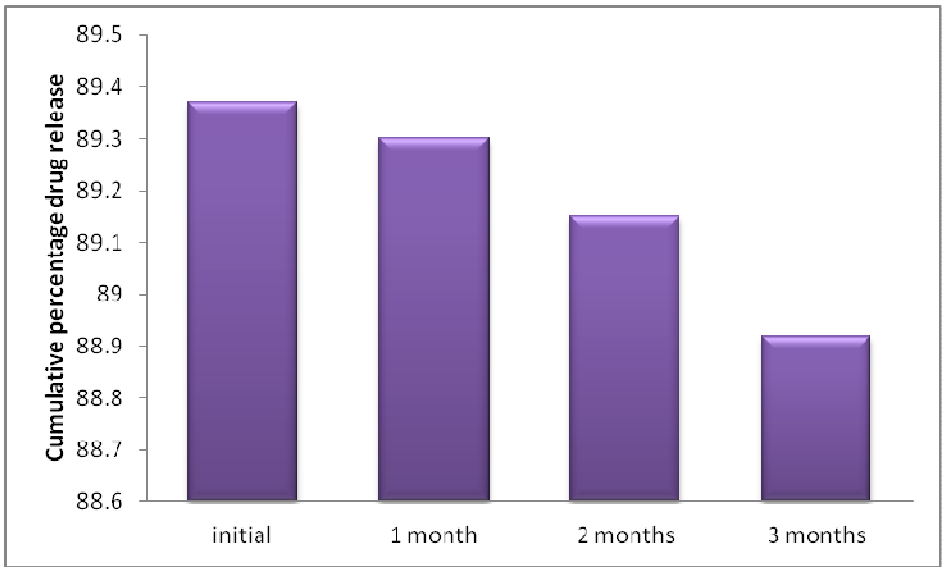


Fig.51. Comparison of cumulative percentage drug released at the end of 12 hours for formulation F7with initial and different periods of stability

No statistically significant differences were observed in percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies. So it can be concluded that the formulation is stable for short term storage conditions.

SUMMARY & CONCLUSION....

10. SUMMARY AND CONCLUSION

A successful colon targeted drug delivery system was developed with the triggering mechanism that responds to the physiological conditions particular to colon.

The colon targeted micropellets of Mebeverine HCl were prepared by using polymers like HPMC K4M, Eudragit L100 and Eudragit S100 for the treatment of IBD. The dissolution study of F7 Micropellets containing Eudragit L100 and Eudragit S100 was concluded the best formulation among other formulations, which showing the most desired drug release. It will be considered as optimized formulation.

The optimized formulation F7 was subjected for stability studies, the formulation was found to be stable in short term stability study.

From the *in-vitro* drug release data, it can be concluded that the HPMC K4M, Eudragit L100 and Eudragit S100 are capable of protecting the drug from being released in Stomach and in Small Intestine. This retardant capacity is more in F7 as compared to other formulations.

During the *in-vitro* drug release study, on exposure to the dissolution fluid, the micropellets slows down further seeping-in of dissolution fluids towards the interior of the pellets. Once the gel layer is formed the drug release takes place mainly by diffusion from the inner region. On reaching the colonic environment the polymeric layer would soluble at colonic pH and release the major amount of drug in the region of colon.

In the *in-vitro* drug release study, the drug release from the micropellets required a longer time in experimental conditions. But in actual use in living systems these limitations for pH environment and it will never be felt. Therefore the micropellets will be take place completely and rapidly in the colon region.

While analyzing the drug release pattern of the drug from the micropellets, it was found that the drug release started in the early hours of study. This was due to change in pH.

Out of the nine formulations, it appears that F7 has the maximum potential in providing colon targeted drug delivery.

FUTURE PROSPECTS....

11. FUTURE PROSPECTS

In this work only physic-chemical characterization and *in-vitro* evaluation of Mebeverine HCl micropellets were done.

1. Along with in-vitro release study in-vivo release studies are also important. So in future in-vivo release study using different models are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.
2. Study the effect of various geometric shapes, in a more excessive manner than previous studies, extended dimensions.
3. Design of novel polymers according to clinical and pharmaceutical need.

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